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AN ATTEMPT TO IDENTIFY THE CENTRAL CELLS MEDIATING KINESTHETIC SENSE IN THE EXTRINSIC EYE MUSCLES *

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At present there is no direct clean-cut anatomic proof that the third, fourth and sixth pairs of cranial nerves are other than purely motor, and anatomic textbooks continue to speak of them only in this way. Anatomically, the inference that they carry kinesthetic sensibility as well is almost overwhelming, but the actual proof is not complete; physiologically, however, it may be regarded as proved.

The anatomic inference that these nerves mediate kinesthetic sense is based largely on the presence of neuromuscular and neurotendinous spindles [1] in the tendinous attachments and bellies of the extra-ocular eye muscles. In other portions of the body, these spindles have been shown [2] to be terminations of about two fifths of the fibers which run in "motor" nerves, the cells of origin of which are in posterior root ganglia. On the physiologic side, Sherrington [3] has published ingenious

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* A preliminary report on this subject appeared in Proc. Soc. Exper. Biol. & Med. **23**:658, 1926.

1. Dogiel, A. S.: Die Endigungen der sensiblen Nerven in den Augenmuskeln und deren Sehnen beim Menschen und den Saugetieren, Arch. f. mikr. Anat. **68**:501, 1906. Huber, G. C., and DeWitt, L. M.: A Contribution on the Motor Endings and on the Nerve Endings in Muscle Spindles, J. Comp. Neurol. **7**:169, 1897. Huber, G. C.: Sensory Nerve Terminations in the Tendons of the Extrinsic Eye Muscles of the Cat, J. Comp. Neurol. **10**:152, 1900. Regaud, C., and Favre: Les terminaisons nerveuses et les organes nerveux sensitifs des muscles striés squelettaux, Rev. gén. d'histol. **1**:1, 1904. Ruffini, O.: On the Minute Anatomy of the Neuromuscular Spindles of the Cat, and Their Physiologic Significance, J. Physiol. **23**:190, 1898-1899. Sutton, A. C.: The Development of the Neuromuscular Spindle in the Extrinsic Eye Muscles of the Pig, Am. J. Anat. **18**:117, 1915. Tozer, F. M., and Sherrington, C. S.: Receptors and Afferents of Third, Fourth and Sixth Cranial Nerves, Proc. Roy. Soc. London **82**:450, 1910.

2. Sherrington, C. S.: On the Anatomic Constitution of Nerves of the Skeletal Muscles: With Remarks on Recurrent Fibers in the Ventral Spinal Nerve Root, J. Physiol. **17**:211, 1894-1895.

3. Sherrington, C. S.: Further Note on the Correlation of the Action of Antagonistic Muscles, Proc. Roy. Soc. London **53**:407, 1893; Further Note on the Sensory Nerves of the Eye Muscles, Proc. Roy. Soc. London **64**:120, 1899; Observations on the Sensual Rôle of the Proprioceptive Nerve Supply of the Extrinsic Ocular Muscles, Brain **41**:332 (Nov.) 1918.

and incontrovertible proof that kinesthetic sense is carried by the third, fourth and sixth cranial pairs; he has substantiated this in part by experiments in nerve degeneration and has been led to the conclusion [4] that "the nervus oculomotorius (and fourth cranial pair) is perhaps not a merely motor nerve, but although purely 'muscular' may be sensorimotor."

It has seemed anomalous also to biologic philosophers that a plurisegmental animal should have paired motor and sensory nerve roots in the spinal and not in the cranial axis. Gaskell [5] and others [6] have studied the peculiar cell residues that occur close to the brain stem in the roots of the third, fourth, motor fifth, sixth and seventh pairs of cranial nerves; these residues, however, are not adequate for mediation of kinesthetic sense.

Degeneration in the nerves of these muscles has also been reported in tabes,[7] which is supposed to be a disease of the afferent system. Available evidence has been discussed by numerous writers, Gast [8] and Nicholls [9] concluding that embryologically, functionally and anatomically the oculomotor is a sensorimotor nerve, while Neal [10] holds that it and its congeners are motor in function.

Because apparent sensory endings are found in the extrinsic muscles of the eyeball, their nerve fibers need not necessarily have cells of origin in the central nuclei of the nerves. The fifth nerve and the sympathetic nerves are in intimate relation with the extra-ocular nerves in the cavernous sinus, and it has been customary to describe anasto-

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4. Sherrington, C. S.: Further Note on the Sensory Nerves of Muscles, Proc. Roy. Soc. London **61**:247, 1897.

5. Gaskell, W. H.: On the Relation Between the Structure, Function, Distribution, and Origin of the Cranial Nerves, Together with a Theory of the Origin of the Nervous System of Vertebrates, J. Physiol. **10**:153, 1889.

6. Kopsch, F.; in Rauber: Lehrbuch der Anat. d. Menschens, part 5, Leipzig, 1907. Nicholson, Helen: On the Presence of Ganglion Cells in the Third and Sixth Nerves of Man, J. Comp. Neurol. **37**:31, 1924. Thomsen, R.: Ueber eigentümliche aus veränderten Ganglienzellen hervorgegangen Gebilde in den Stammen der Hirnnerven des Menschen, Virchows Arch. f. path. Anat. **109**:459, 1887. Tozer, F. M.: On the Presence of Ganglion Cells in the Roots of the Third, Fourth and Sixth Cranial Nerves, J. Physiol. **45**:xv, 1912.

7. Oppenheim, H., and Siemerling, E.: Beiträge zur Pathologie der Tabes dorsalis under der peripherischen Nervenkrankung, Arch. f. Psychiat. **18**:98, 1887.

8. Gast, R.: Die Entwicklung des Oculomotorius und seiner Ganglien bei Selachierembryonen, Mitth. Zool. Stat. Neap. **19**:269, 1909.

9. Nicholls: On the Occurrence of An Intracranial Ganglion on the Oculomotor Nerve in the Scyllum Canicula, Proc. Roy. Soc. London, series B, **88**:553, 1915.

10. Neal, H. V.: The Morphology of the Eye Muscle Nerves, J. Morphol. **25**:1, 1914.

moses between nearly all five sets of fibers; in fact, Morat [11] states that the fifth nerve carries muscle sense for the extra-ocular muscles. For another possible type of distribution, Langworthy [12] has recently shown that the peripheral sensory fibers of the hypoglossal nerve reach the cerebrospinal axis largely by way of the ansa hypoglossi and the second cervical posterior root. Again, Streeter [13] has shown Froriep's ganglion cells scattered along the eleventh and twelfth nerves.

There is much conflicting detail reported even in the actual origin, anastomosis, and anatomic distribution of the fibers composing the peripheral trunks of the third, fourth and sixth nerves. None of the work is exhaustive, much of it is contradictory, and nowhere is it adequately correlated in the literature. In general, it may be said that Brouwer's [14] work on the third nucleus assembles or refers to most of the antecedent investigations, and that Spiller's [15] recent case further confirms Brouwer's suggested distribution of the subnuclei; other papers on this subject and on the fourth and sixth nuclei are available.[16] The peripheral nerves have been studied by van der Scheuren,[17] Sherrington and Tozer,[18] and others;[19] as have also the terminal distributions and

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11. Morat, J. P.: Physiology of the Nervous System, translated by H. W. Syers, Chicago, W. T. Keener & Co., 1906.

12. Langworthy, O. R.: Problems of Tongue Innervation: Course of Proprioceptive Nerve Fibers, Autonomic Innervation of Skeletal Musculature, Bull. Johns Hopkins Hosp. **35**:239 (Aug.) 1924.

13. Streeter, G. L.: The Development of the Cranial and Spinal Nerves in the Occipital Region of the Human Embryo, Am. J. Anat. **4**:83, 1904.

14. Brouwer, B.: Klinisch-anatomische Untersuchung über den Oculomotoriuskern, Ztschr. f. d. ges. Neurol. u. Psychiat. **40**:152, 1918.

15. Spiller, W. G.: Ophthalmoplegia Internuclearis Anterior: A Case with a Necropsy, Brain **47**:345 (Aug.) 1924.

16. Duval, M., and Laborde, J. V.: De l'innervation des mouvements associés des globes oculaires: études d'anatomie et de physiologie expérimentelle, J. de l'anat. et de la physiol. **16**:56, 1880. Hunter, J. I.: The Oculomotor Nucleus of Tarsius and Nyctecebus, Brain **46**:38 (May) 1923. Malone, E. F.: Efferent Characteristics of Reception Centers, Science **57**:449, 1923. Tsuchida, U.: Ueber die Ursprungskerne der Augenbewegungensnerven und über die mit diesen in Beziehung stehenden Bahnen in Mittelhirn und Zwischenhirn, Arb. a. d. hirnanat. Inst. Zurich **2**, 1906. Van Gehuchten, A.: Anatomie du système nerveux de l'homme, ed. 3, Louvain, Uystpruyst, 1900, vol. 2. Barker, L. F.: The Nervous System and Its Constituent Neurones, New York, D. Appleton & Co., 1901. Bernheimer, S.: Zur Kenntnis der Lokalisation im Kerngebiete des Oculomotorius, Wien. klin. Wchnschr. **9**:767, 1896.

17. Van der Scheuren, A.: Le degré d'entrecroisement des nerfs moteurs du globe oculaire, Le Névraxe **10**:119, 1908.

18. Sherrington and Tozer (footnote 1, seventh reference).

19. Barratt, J. O. W.: Observations on the Structure of the Third, Fourth and Sixth Cranial Nerves, J. Anat. & Physiol. **35**:214, 1901. Bischoff:

endings.[20] A detailed evaluation of these conflicting data is beyond the scope of this paper.

METHOD OF STUDY

Histologic.—Work was undertaken, first, to determine whether the cells mediating impulses from the neuromuscular and neurotendinous spindles of the extra-ocular muscles were located outside the brain stem in detectable nidi.

The intra-vitam methylene blue technic of Ehrlich, as given by Wilson,[21] was used on several embryo pigs, from 15 to 16 cm. long; the eye muscles were then dissected out and examined in glycerine picrate solution. In adult dogs the orbital contents, largely freed from gross fat, were dissected out with the complete extra-ocular nerves. These contents were then fixed in Müller's fluid, to which 10 per cent acetic acid had been added; they were then preserved in alcohol, stained either with alum cochineal or Mayer's carmalum, and then teased in a preservative glycerine bath under observation with a high power binocular microscope. A series of minute dissections under physiologic sodium chloride solution was made on cats' and dogs' heads, both fixed and fresh material being utilized, in an attempt to demonstrate macroscopic anastomotic trunks.

Mikroscopische Analyse der Anastomosen der Kopfnerven, Munich, 1865. Boeke, J.: Die doppelte (motorische und sympathische) efferente Innervation der quergestreiften Muskelfasern, Anat. Anz. **44**:343, 1913; Studien zur Nervenregeneration: II., Verhandl. d. K. Akad. v. Wetensch. **19**:1, 1917. Carpenter, F. W.: The Development of the Oculomotor Nerve, the Ciliary Ganglion, and the Abducens Nerve in the Chick, Bull. Mus. Comp. Zool., Harvard College **48**:139, 1906. Carpenter, F. W., and Conel, J. L.: A Study of the Ganglion Cells in the Sympathetic Nervous System with Especial Reference to Intrinsic Sensory Neurones, J. Comp. Neurol. **24**:269, 1914. Gray: Textbook of Anatomy, Descriptive and Applied, ed. 21, London, Longmans Green & Co., 1920. Koch, S. L.: On the Structure of the Third, Fourth, Fifth, Sixth, Ninth, Eleventh and Twelfth Cranial Nerves, J. Comp. Neurol. **26**:541, 1916. Kuntz, A.: The Development of the Sympathetic Nervous System in Man, J. Comp. Neurol. **32**:173, 1920. Macalister: Text of Human Anatomy, London, Griffin, 1889. Marinesco, G.; Parron, and Goldstein: Sur la nature du ganglion ciliare, Comp. rend. Soc. de Biol. **1**:88, 1908. Raeder, J. G.: "Paratrigeminal" Paralysis of Oculopupillary Sympathetic, Brain **47**:149 (May) 1924. Whitnall, S. E.: Anatomy of Human Orbit, Oxford Medical Publications, 1921. Wilson, J. T.: Double Innervation of Striated Muscle, Brain **44**:233 (July) 1921. Zoth, O.: Augenbewegungen und Gesichtswahrnehmungen, Handb. Physiol. Menschen (Nagel) **3**:283, 1905.

20. Ciaccio, G. V.: Sur les plaques nerveuses finales dans les tendons des vertébres, Arch. Ital. de Biol. **14**:31, 1891. Harrison, P. W.: An Attempt to Determine the Sensory Path from the Ocular Muscles, Bull. Johns Hopkins Hosp. **20**:113, 1909. Huber, G. C.: Observations on the Degeneration and Regeneration of Motor and Sensory Nerve Endings in Voluntary Muscle, Am. J. Physiol. **3**:339, 1900.

21. Wilson, J. G.: Intra-Vitam Staining with Methylene Blue, Anat. Rec. **4**:267, 1910.

In the degeneration experiments, the brain of an animal killed in a few seconds with an overdose of chloroform and fixed for four days in 95 per cent alcohol, in another four days was dehydrated and then run through xylol, xylol-cedar and cedar-oil-paraffin into several baths of pure paraffin; it was embedded, sectioned serially at 30 or 50 microns from the interpeduncular region to the obex and mounted on Mayer's egg albumin by the water flotation method; it was then stained for from three and one half to four hours in fresh 1 per cent aqueous toluidin blue at from 38 to 42 C., differentiated in several changes of 95 per cent alcohol, under observation with the microscope and mounted in xylol balsam. The cat's brain and also one of the dogs' brains were sectioned in celloidin in the customary manner, as recommended by Nissl. In each case the third, fourth and sixth pairs of cranial nerves were carefully dissected out from the brain stem to the muscle, kept moist with the animal's serum, mounted on blotters, sketched, measured and prepared by the Campbell[22] technic, which allows simultaneous demonstration of myelinated and unmyelinated fibers and has the advantage of allowing counterstaining in addition (Ehrlich's hematoxylin and alcoholic eosin were used). Several short series of sections at 10 microns of each of these nerves were taken every 8 or 10 mm. along the nerve, at branchings and anastomoses and at other interesting points. The peripheral nerve fibers and the cell nucleoli in the brain stem were counted on a mechanical stage, by means of a Spencer 4 mm. objective and a 6 × or 10 × ocular containing a micrometer and a square apertured diaphragm; the fibers were classified according to size and type and the cells according to location, subnuclei, size and degeneration.

Operative Technic.—Since adequate methods of approach for operative section of the extra-ocular nerves near the brain stem were learned only after several attempts, those finally worked out are outlined, largely because they are not already in the literature, with the exception of the brief account by Harrison (and Cushing).[23] The animals must live for from sixteen to eighteen days after operation; the strictest aseptic technic, therefore, should be used.

Operation for Third Nerve Section: After slow intravenous injection of from 1 to 1.3 Gm. of sodium chloride per kilogram of body weight, in the form of 35 per cent aqueous solution, ether anesthesia is started; the head is shaved, the skin sterilized with benzol and alcoholic iodine or mercurochrome-220 soluble, and a crescentic incision is made along the upper border of the temporal muscle from the anterior end of the zygomatic process to the base of the ear. The temporalis is cut along the edge of the temporal fossa, and the muscle is freed from its bony attachment with a sharp periosteal elevator; its posterior half is excised, the anterior half retracted anteriorly and the muscle freed well down to its attachment to the ramus of the mandible. A 2 cm. trephine opening is made, with its lower edge just above the zygomatic process, this opening being enlarged to the base of the middle fossa with rongeurs, and the intact dura is stripped from the bone on the base of the skull until its strong attachment just before the gasserian ganglion is reached. Here the

22. Campbell, Helnor: A Differential Stain for Nerve Fibers, Mil. Surgeon **51**:11, 1922.

23. Harrison (footnote 20, first reference).

dura is caught with a small dura hook and a small linear opening is made and enlarged with fine scissors, a curved spatula introduced and the shrunken brain retracted upward and toward the midline. The shining white cord of the third nerve is then plainly in view and can be divided with scissors as close to the brain stem as desired. This method does not require a contralateral decompression operation; the point is that the dura is not opened until the midline is nearly reached. Ptosis and pupillary dilation confirm the operation.

Operation for Fourth Nerve Section: After a similar preliminary treatment and exposure of the skull, the trephine opening is again enlarged to the base of the middle fossa, slightly more posteriorly than before, and the dura is freed to about the lowest portion of the fossa. Here a linear opening is made and a minute, scythelike knife, set at right angles to a long malleable handle, is introduced; this is passed backward, upward and medially until the knife is felt to fall over the edge of the tentorium; it is then withdrawn against resistance for from 2 to 3 mm., elevated slightly and withdrawn. This operation has the disadvantage of not being done under direct vision, and, furthermore, does not sever the nerve before the reception of the supposed meningeal fascicle, which in the dog is only 7 or 8 mm. from the origin of the fourth nerve. A cerebellar approach is contemplated, but has not been worked out.

Operation for Sixth Nerve Section: Two hours after being given 2 cc. of fresh paraldehyde per kilogram of body weight by stomach tube, the animal is placed on its back on the table and its head held steady, with widely retracted jaws and protruded tongue, by suitable devices. The soft palate is incised almost to its posterior border and lateral retraction obtained by guy sutures. The nasopharynx is cleaned with dry and mercurochrome swabs; the tympanic bullae and anterior rim of the foramen magnum are palpated, and a midline incision of the nasopharyngeal mucosa is made, from 20 to 25 mm. long, the mucosa being freed from the desired side and tacked with silk to the retracted soft palate. The basal plate of the occipital bone is then attacked either with the surgical engine or with gouge and mallet, an opening being made from the midline laterally for from 10 to 11 mm., and from the anterior margin of the tympanic bullae to about 10 or 12 mm. anterior to the rim of the foramen magnum. When chisel and mallet are used, the troublesomely vascular, thick diploe is controlled by bone wax; in the lateral border of the bony incision the inferior petrosal sinus may be encountered, but this also can readily be controlled by wax. After careful exposure of an area from 8 to 10 mm. in diameter, absolute hemostasis being established, the sixth nerve is seen dimly, shining through the dura, running laterally and anteriorly from the inferior border of the pons. The dura is caught with the dura hook and adequately incised; a cutting hook is introduced and the nerve severed under direct vision. The pharyngeal mucosa is partially closed anteriorly only, the soft palate completely in layers. For several days afterward, the head should not be lowered much, as acute loss of cerebrospinal fluid may constrict the medulla and cerebellum in the tentorial opening; it may be necessary to feed the animal by tube with sugared egg-nogs for several days because of its unwillingness to swallow. This operation is a modification of that of Pollock and Davis.[24] Of the several animals successfully operated on, all have died following subsequent unforeseen laboratory errors; results are not here reported; the operation itself, however, has demonstrated its adequacy.

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24. Pollock, L. J., and Davis, L. E.: Studies in Decerebration, Arch. Neurol. & Psychiat. **10**:391 (Oct.) 1923.

OBSERVATIONS

Fibers.—Peripheral Nidi: The intra-vitam methylene blue stain, though affording orientation, produced no pertinent results. When the nerves stained with carmalum were teased, no aberrant cells were found anywhere along the course of the third nerve in one dog; a second dog had two or three ganglion cells on the nerve branch to the left inferior oblique muscle, and eight ganglion cells about 6 mm. from its apparent "insertion" into the belly of the right inferior oblique muscle. This dog also had two small accessory ganglia on the short ciliary nerves of the right side; the other two dogs each showed groups of seven or eight cells at the extreme central end of the right and left

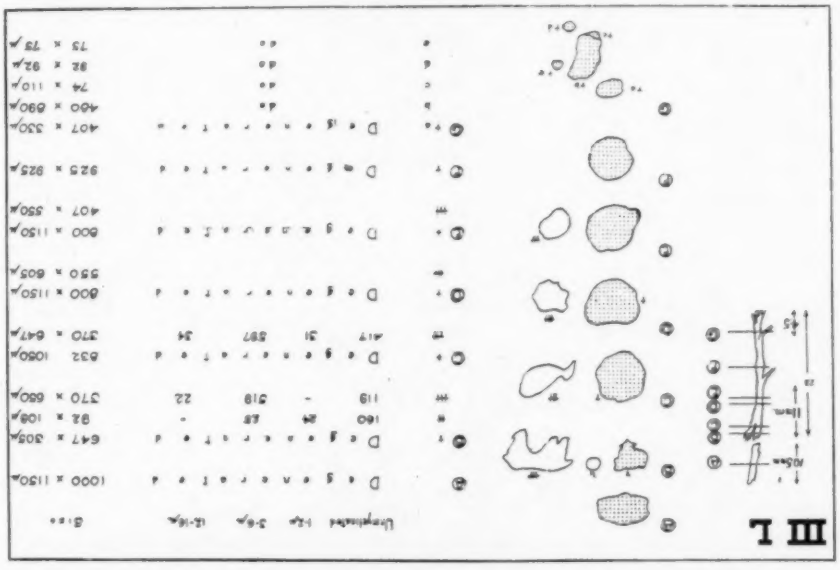

Fig. 1.—Topographic summary of the results of fiber counts in the extramedullary portion of the left third nerve of dog C 4. A sketch of the gross nerve, with measurements, is shown first, this acting as a key figure for the drawings of the cross-sections of the preparation at the level indicated, while the statistical columns show the numbers of fibers in each section, arranged according to cross-section diameter of the fibers. Degeneration is represented by stipples.

third nerves, respectively. The trochlear nerves were entirely without aberrant ganglion cells. The abducens nerve was likewise free, except in the case of the dog mentioned above as having aberrant cells on the branches to the inferior oblique muscles; the right sixth nerve of this dog showed several dubious ganglion cells at its entrance to the orbit, near the crotch of a small filament given off to an unascertainable destination at that point; in this dog also, one or two ganglion cells were

found embedded in the rootlets of the central end of one sixth nerve. None of these observations were constant enough, nor found often enough to warrant their further investigation or possible cells of origin for the numerous sensory endings in the extra-ocular muscles.

Anastomoses: The repeated attempts at minute gross dissection of the nerves in situ in a saline bath merely revealed the inadequacy of the method. When the (left) third nerve was sectioned 10.5 mm. from the brain stem (dog C 4), microscopic examination of prepared specimens showed that all the fibers, both distal and proximal to the lesion, were degenerated (fig. 1). Anastomotic connections with any portion

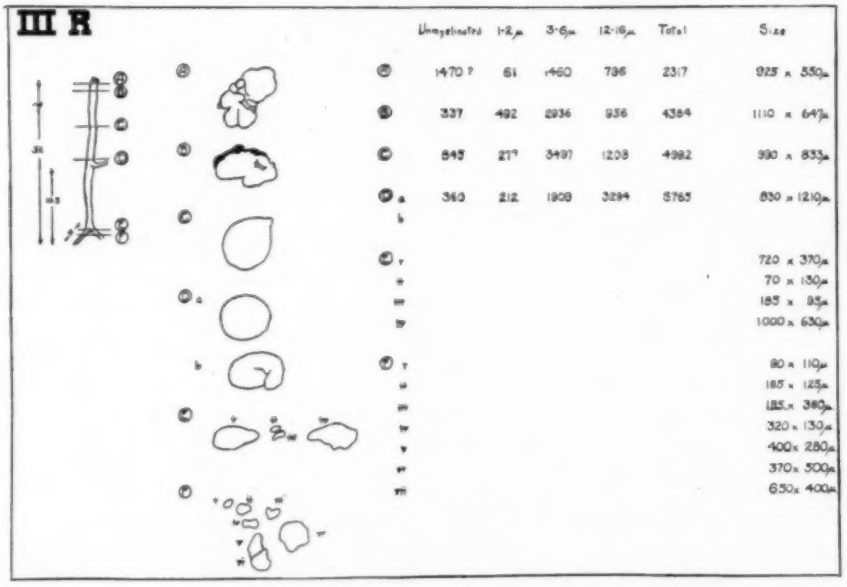

Fig. 2.—Topographic summary of the results of fiber counts in the extramedullary portion of the right third nerve of dog C 4, seventeen days after section of the left third nerve. The arrangement is the same as in figure 1. The solid shading shows the location of Thomsen's cell residues.

of the fifth nerve were not found. Although unmyelinated fibers were found in and close under the sheath of the nerve, as well as sparsely scattered throughout the trunk, neither the two small transiently associated unmyelinated bundles noted by Koch [25] nor, in the sections cut, any acquisition of fibers from the plexus caroticus internus were found. It was impossible to make out the persistence of unmyelinated fibers in the distal portions of the severed nerve, owing to the fact that the shreddy neurofibrils which remained confused the picture.

25. Koch (footnote 19, eighth reference).

Both right and left fourth nerves showed acquisition of a finely myelinated branch close to their origin; these were at first discrete and later adherent to the nerves, and still later, through the disappearance of the fibrous intervening septum, sank peripherally into intimate relation with other fibers of the trunk, as noted by Barratt;[26] these fibers were not seen to leave the nerve. Although this branch is probably the recurrent meningeal nerve of Arnold, from the ophthalmic branch of the fifth, it is being investigated further. Barratt's two fine fascicles, transiently present in man, were not observed by Koch[25] in the dog, nor were they found in the present material. A few (from 3 to 72)

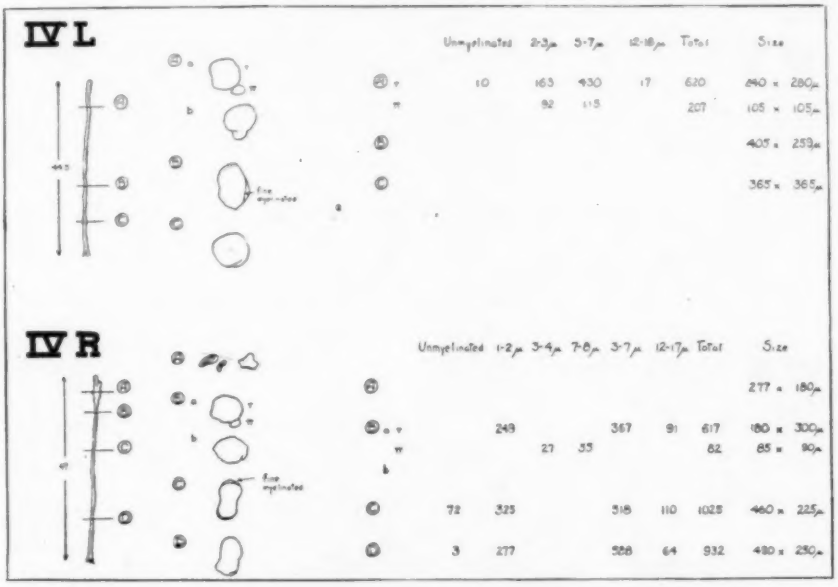

Fig. 3.—Topographic summary of the results of fiber counts in the extramedullary portion of the right and left fourth cranial nerves of dog C 4, seventeen days after section of the left third nerve. The arrangement is the same as in figure 1. The stipples again represent degeneration; the left fourth nerve was injured trivially in the cavernous sinus region at the time the third nerve was sectioned; although an unimportant injury it nevertheless vitiates the peripheral portion of the nerve for statistical purposes.

unmyelinated fibers were seen close under the sheath of the nerve; it is possible that some of these are the fibers found more peripherally by Boeke.[27]

In the sixth pair, connection with the fifth nerve again was not demonstrated, although in the case of the right sixth nerve their inti-

26. Barratt (footnote 19, first reference).

27. Boeke (footnote 19, fourth reference).

mate relation was followed (fig. 4). Only one of Barratt's fine medullated-fiber fascicles was found, although both of Koch's unmyelinated bundles were seen; in this case, however, the latter did not form intimate (subcapsular) relationship, but nevertheless did leave the trunk at about its entrance to the orbit; a few unmyelinated fibers persisted in the trunk from the nerve's origin to the most distal section.

Thomson's Residues: In the sections of the third nerve, Gaskell's [5] amorphous material was noted (fig. 2 *B*).

Degeneration: When the left third nerve is sectioned, all the fibers seen in the trunk, both distal and proximal to the lesion, appear degenerated.

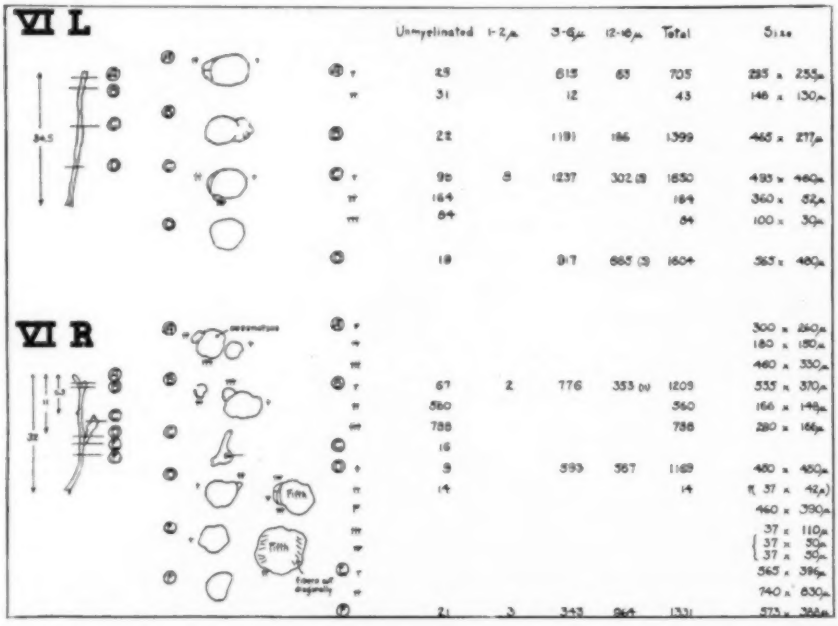

Fig. 4.—Topographic summary of the results of fiber counts in the extramedullary portion of the right and left sixth cranial nerves of dog C 4, seventeen days after section of the left third nerve. The arrangement is the same as in figure 1. The intimate relation of the fifth nerve is followed in the sections of the right sixth nerve.

Dichotomy: This apparently occurs in the peripheral trunks of the nerves, as shown by statistics given in figures 1 to 4. Here is shown a steady increase in counted numbers of fibers in the third nerve (fig. 2) as one progresses peripherally, and in the fourth and sixth nerves for at least the first 10 mm. of the trunk's course outside the brain stem. In the fourth nerve apparent direct evidence of dichotomy was found in several sections, in which two axis-cylinder bundles were enclosed in a

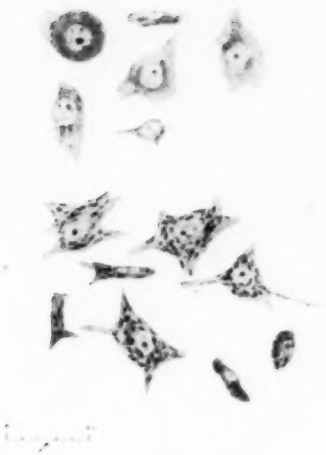

Fig. 5.—Cells of fourth and sixth nucleus, dog C 4: The three cells in the upper half of the figure are from the fourth nucleus. Those in the lower half are from the sixth nucleus, both large and small type cells being shown. The right hand cell in the top row of the sixth nucleus cells is the peculiar type of "combed feltwork" mentioned in the text.

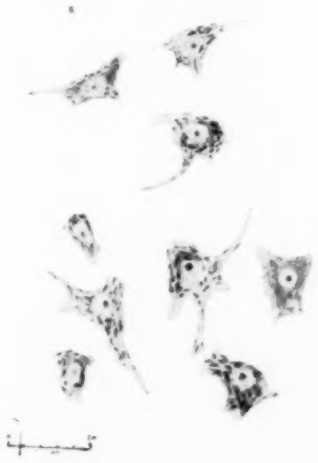

Fig. 6.—The three large drawings at the top were obtained by posting on a large sheet of cross-section paper the cell count for each individual section in the entire series for the third nucleus in dog C 4, and then drawing smooth curves through mean points. The normal or intact cells are represented by solid lines, and the degenerated cells by broken lines — the left third nerve in this dog having been severed seventeen days. The scales given allow quantitative interpretation of the figures. It should be noted that the number of intact cells apparently exceeds the degenerated ones, this being particularly true in the smaller group. The possible significance of this is considered in the text. The actual appearance of the nucleus in cross-section view at various levels is shown in the small drawings A to L, the "total cells" drawing above acting as the key figure for the levels represented. The Edinger-Westphal nucleus is represented as stippled, and the nucleus supratrochlearis as small circles in I to J, the latter nucleus continuing caudad but not being shown in K to L. The attempt to divide the nucleus into subgroups often appears arbitrary, as in the region E and again posteriorly. The lined field in H and I represents sparse distribution of cells.

single sheath, slightly distal to large bundles in single sheaths, in a region in which the cross-section count of fibers was increasing. Careful estimations in dog C 8 indicate a similar result. Willems [28] has demonstrated substantially the same situation for the trigeminal nerve. Not only does the number of fibers increase, but also the degree of myelinization increases steadily in these nerves throughout their course.

Central Nuclei.—Cell Size: Preliminarily, a comparison of a series of scaled drawings of cells from serial Nissl sections of the brain of

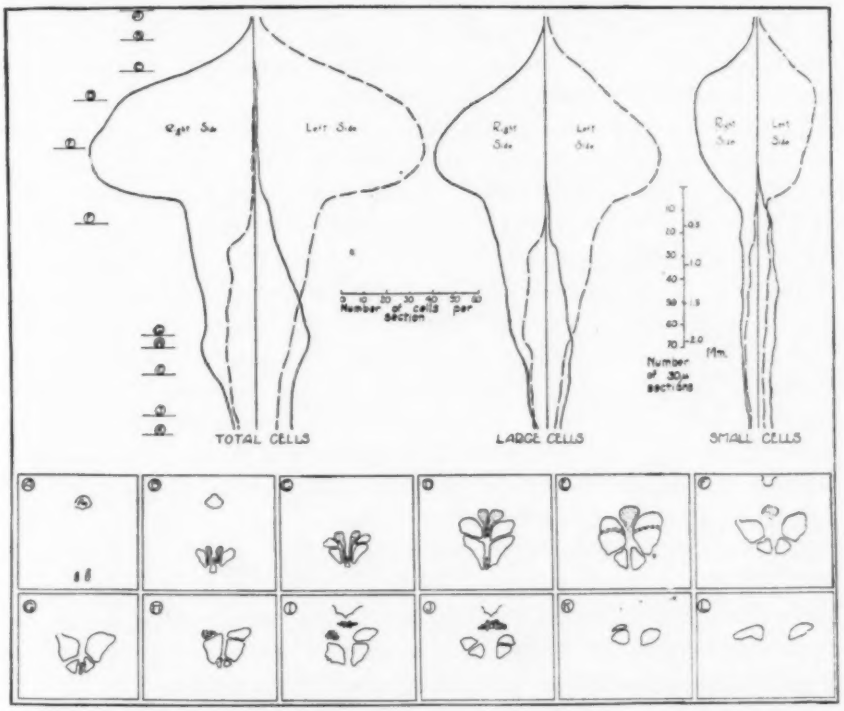

Fig. 7.—Cells of third nucleus, dog C 4: Those in the upper portion of the figure are degenerated cells from the left side of the nucleus seventeen days after section of the nerve. Those in the lower half of the figure are intact cells. Both large and small type cells are shown. The scale in the corner allows measurement of the cells (one division equals 10 microns). Camera lucida drawings.

the cat failed to show groups according to any cell characteristic other than size. Two fairly distinct groups were discerned, both having the Nissl substance collected into typical "motor" rhombs and wedges. The

28. Willems, E.: Localisation motrice et kinesthétique (chez le noyau masticateur et mesencéphalique du trijumeau chez le lapin), Le Névraxe **12**: 9, 1911.

smaller cells, about 10 by 16 microns, were less in number than the large ones (27 by 36 microns). In the dog, the smaller ones are from 20 to 25 by from 10 to 15 microns, the larger from 30 to 40 by from 20 to 30 microns (figs. 5 and 6), although no perceptible difference in any character of Nissl substance, cytoplasm, hillock, nucleus or nucleolus (4 microns in diameter in both) could be determined. The small cells are in general arranged about the nuclear groups as a shell, usually denser dorsally, although at times they are diffusely commingled with the large cells throughout the nucleus. Tabulations and charts not here presented show that the small cells do not preponderate in any portion of the third, fourth or sixth nuclei, nor in any of the subnuclei of the third nucleus, except Perlia's median nucleus which, in the dog, is made up entirely of these smaller cells.

Subnuclei: An attempt was made to divide the third nucleus into dorsal and ventral, and anterior and posterior, nuclei—four to a side—in addition to Edinger-Westphal, Perlia, and trochlear nuclei, after Jacobsohn.[29] This may be possible in man, but Kappers'[30] division of the lateral nuclei into dorsolateral and ventromedian subnuclei is better in the dog. The median (Perlia) nucleus is not well developed in the dog; it starts shortly after the lateral subnuclei, and extends raggedly through a little more than three fifths of their extent. The Edinger-Westphal nucleus, starting in a deeply ventral position, rises rapidly dorsally and caudad until it surmounts the lateral subnuclei; casual examination of it in dog C 4 showed the expected unilateral chromolytic changes. Although it is stated that the division between the third and fourth nuclei in man is definite,[29] this has not been found true for the rabbit,[17] and is not true for the dog; great difficulty was encountered in effecting this separation, but within from 0.4 to 0.6 mm. the change is clear; within this distance the remnant of the third nucleus apparently rises dorsally and the globular fourth nucleus insinuates itself beneath, considerable admixture of cells, however, being present.

Degeneration: When the third nerve is sectioned close to the brain stem, almost half of the total number of cells in the third nucleus show unequivocal signs of Nissl degeneration. This degeneration, as shown qualitatively by numerous others, is at first (cephalad) solely homolateral, then increasingly bilateral and, as more recent work has shown in the rabbit[17] and in these experiments in the dog, never becomes (caudad) solely contralateral; the exact distribution of these cells in dog C 4 is shown in figure 7. A statistical tabulation given in table 1

29. Jacobsohn, L.: Ueber die Kerne des menschlichen Hirnstamms, Abhandl. d. K. Preuss. Akad. d. Wissensch. **2**:1, 1909.

30. Kapers, C. U. A.: Die vergleichende Anatomie des Nervensystems der Wirbeltiere und des Menschen, Harlem, De Erven F. Bohn, 1920, p. 550.

TABLE 1.—*Consolidation of Actual Section Cell Counts in the Third Nucleus of Dog C 4*

Right								Left								Median		Right				Left				Right	Left	Degenerated						Intact						Totals
Dorsal				Ventral				Dorsal				Ventral						Large		Small		Large		Small				Right				Left				Totals						
Large		Small		Large		Small		Large		Small		Large		Small																											
Norm.	Deg.	Norm.	Deg.	Norm.	Deg.	Norm.	Deg.	Norm.	Deg.	Norm.	Deg.	Norm.	Deg.	Norm.	Deg.	Norm.	Deg.	Norm.	Deg.	Norm.	Deg.	Norm.	Deg.	Norm.	Deg.			Large	Small	Large	Small	Large	Small	Total	Large	Small	Large	Small	Large	Small	Total
Col. 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
Derivation																		2 + 6	3 + 7	4 + 8	5 + 9	10 + 14	11 + 15	12 + 16	13 + 17	20 + 22	21 + 23	24 + 26	25 + 27	28 + 29	30 + 31			21	23	25	27	34 + 36	35 + 37	38 + 39	20	22	24	26	41 + 43	42 + 44	45 + 46
9	...	..	...	..	11	..	34	1	...	...	..	...	..	21	2	48	..	..	11	..	34	1	..	21	2	48	45	1	2	69	46	71	..	1	21	48	21	49	70	11	34	..	2	11	36	47
15	32	1	39	—	112	—	182	2	2	48	9	26	—	109	10	195	13	24	144	1	221	2	2	217	19	221	365	3	• 21	438	368	459	1	2	217	221	218	223	441	144	221	2	19	146	240	386
15	138	1	109	—	207	2	183	1	1	147	1	109	2	209	5	194	8	22	345	3	292	1	3	356	6	303	637	4	9	659	641	638	3	1	356	303	359	304	663	345	292	3	6	348	298	646
5	69	1	44	—	95	—	90	1	1	53	1	59	1	79	1	97	2	12	164	1	134	1	2	132	2	156	298	2	4	288	300	292	1	1	132	156	133	157	290	164	134	2	2	166	133	302
15	411	1	164	1	260	—	182	1	4	421	11	127	—	303	1	180	20	4	671	1	346	2	4	724	12	307	1017	3	16	1031	1020	1047	1	2	724	307	725	309	1034	671	346	4	12	675	358	1033
17	443	1	173	1	281	—	197	1	6	452	12	136	—	324	1	188	20	4	724	1	370	2	6	776	13	324	1094	3	19	1100	1097	1119	1	2	776	324	777	326	1103	724	370	6	13	730	383	1113
23	373	15	78	5	164	4	87	1	24	316	61	40	11	242	33	64	48	10	537	19	165	6	35	558	94	104	702	25	129	662	727	791	19	6	558	104	577	110	687	537	165	35	94	572	259	831
14	173	70	44	26	131	49	49	22	48	192	43	15	33	158	39	43	43	17	304	119	93	48	81	350	82	58	397	167	163	408	564	571	119	48	350	58	469	106	575	304	93	81	82	385	175	560
14	111	41	49	18	132	65	52	18	45	103	43	14	57	136	70	34	24	6	243	106	101	36	102	239	113	48	344	142	215	287	486	502	106	36	239	48	345	84	429	243	101	102	113	345	214	559
14	121	60	40	19	56	62	41	30	90	106	55	39	55	61	69	13	20	5	177	122	81	49	145	167	124	52	258	171	269	219	429	488	122	49	167	52	289	101	390	177	81	145	124	422	258	680
14	152	58	67	50	81	37	52	35	119	85	64	40	70	35	75	28	4	—	233	95	119	85	189	120	139	68	352	180	328	188	532	516	95	85	120	68	215	153	368	233	119	189	139	422	258	680
14	30	32	17	24	56	81	54	57	47	30	48	26	54	48	96	35	4	1	86	113	71	81	101	78	144	61	157	194	245	139	351	384	113	81	78	61	191	142	333	86	71	101	144	187	215	402
14	23	14	24	22	66	72	71	53	26	14	45	22	84	37	76	54	—	2	89	86	95	75	110	51	121	73	184	161	231	127	345	358	86	75	51	76	137	151	288	89	95	110	121	199	216	415
				69	40	71	39					46	25	92	31			69	40	71	39	46	25	92	31	140	79	138	56	219	194			40	39	25	31	65	70	135	69	71	46	92	115	163	278
Totals																		3797	707	2193	428	823	3814	963	1857	5990	1135	1809	5651	7125	7460	707	428	3814	1857	4521	2285	6806	797	2193	826	963	4623	3156	7779

* In the table, one horizontal line represents one large slide, the number of sections to a side being shown in column 1. Columns 2 to 19 are the figures of the actual counts as made with the microscope. All columns from 20 on are various statistical aggregations and digests developed from columns 2 to 19 in the manner shown in the line "Derivation" (e. g., column 20 is the sum of columns 2 and 6; column 28 is the sum of columns 20 and 22). The purposes of the consolidations are evident from the highest column headings.

Peculiar Cell Types: In several sections of the degenerated central nuclei, large, blurred-Nissl binucleate cells were encountered. Whether these were evidences of regeneration, as thought by Tedeschi,[31] or giant neuroglia cells or fibroblasts, could not be determined.

A peculiar type of cell "not of strict motor type," noted by Jacobsohn [29] in the caudal portion of the sixth nucleus in man, was encountered occasionally in the sixth nuclei of both dog C 4 and C 8; its large cytoplasm stained with toluidin blue to give the effect of a combed feltwork uniformly distributed (fig. 6). His "zarter" and the ordinary "motor" type cells were present also.

Contiguous Structures: The nucleus supratrochlearis was carefully examined for evidence of degenerated cells, but none was found.

COMMENT

Statistical Correction.—In an endeavor to find some statistical correlation between the numbers of large and small cells already noted as being in the nucleus and the numbers of large and small fibers in the nerve trunks, careful counts of cells and fibers were made. This was done with the hope of correlating a type of fiber with a type of nerve ending—as has been done [2] inferentially in the spinal nerves— and this in turn with a certain size or a certain type of cell in the central nucleus.

In order to approach complete accuracy as closely as possible, only nucleoli of cells were counted; because of strict adherence to this criterion, it is believed that some cells in which degeneration had advanced as far as nuclear chromatolysis have not been included; it is probably because of this that the number of degenerated cells does not quite equal that of intact cells (table 1). Check counts of the same sections at different times, both in regard to fibers in the peripheral trunks and cells in the nuclei of origin, showed regularly a check accuracy of from 5 to 9 per cent.

In the case of the cells of its central nuclei, however, another correction also must be considered: In a complete series of sections, nucleoli will often be cut so as to leave one part of the nucleolus in one section and the other in another. In this manner the same nucleolus is counted twice. The intact nucleoli in the third, fourth and sixth nuclei of these dogs were uniformly close to 4 microns in diameter, and when cut so that only about a fourth of one remained in a section, the resulting segment, obviously small, appeared poorly stained and was not counted. If mathematically a nucleolus is considered as really belonging to a given section if its center falls within that section, it is clear that all which belong to any section will be counted in that section, together

31. Tedeschi, A.: Anatomisch-experimentelle Beitrag zum Studien der Regeneration des Gewebe des Centralnervensystems, Beitr. z. Path. Anat. u. d. allg. Path. **21**:43, 1897.

with some that belong to the section preceding or to the section following. A cut nucleolus will be counted in a 30 micron section if the distance of its center outside the section is not greater than 1 micron; and thus in a 30 micron section all nucleoli (whole or cut) that "belong" within a distance of 32 microns will be counted. If the nucleoli are almost evenly distributed throughout, the count in each section will be thirty-two thirtieths as great as the number actually belonging to the section. A trivial correction for the outer faces of the first and last sections is also necessary (if the first section was so cut that it barely included the earliest nucleoli, their centers would be 2 microns from the first face, and the nucleoli "belonging" to this first section would range through only 28 instead of 30 microns). Thus the count in the various sections would run:

$$\begin{aligned}
\text{Count of 1st:}\quad & N_1 + 1/30\,N_2 \\
\text{2d:}\quad & N_2 + 1/28\,N_1 + 1/30\,N_3 \\
\text{3d:}\quad & N_3 + 1/30\,N_2 + 1/30\,N_4 \\
\text{etc.}\quad & - - - - - - - - \\
\text{n-1:}\quad & N_{n-1} + 1/30\,N_{n-2} + 1/28\,N_n \\
\text{n:}\quad & N_n + 1/30\,N_{n-1}
\end{aligned}$$

The total count would be:

Total count

$$\begin{aligned}
(c) &= (N_1 + N_2 + \ldots + N_n) + 2/30\,(N_2 + N_3 + \ldots + N_{n-1}) + 1/28\,(N_1 + N_n) \\
&= (\text{total number}) + 1/15\,(\text{total number}) - (1/15 - 1/28)\,(N_1 + N_n) \\
&= 16/15\ \text{total number} - 13/420\,(N_1 + N_n) \\
T &= 15/16\,(C + [13/420\,(N_1 + N_n)])
\end{aligned}$$

The changes for other sizes of nucleoli or other thickness of section are obvious; the correction for the first and last sections may be disregarded (seldom more than one cell correction), and it may be said in general that the total count is the following fraction of the actual number of cells present:

$$C = \frac{\text{thickness of section in microns} + (\text{nucleolar diameter} - 2\ \text{microns})}{\text{thickness of section in microns}}$$

The figures given in table 1 are consolidations of actual cell counts; those for cells in table 2 and those given for cells in the text are figures corrected according to the foregoing formula.

Correlation.—(*a*) Material: For correlation, it is of course apparent that the fiber counts should not be taken in the first fractions of a millimeter of the proximal end of the nerve, for here it is conceivable that even with careful handling, the fibers might break or shrink unevenly longitudinally while being cut or in the fixing fluids, and that all the fiber tips might not be represented accurately in the first few hundred serial sections; at a distance of 2 or 3 mm., however, this source

of error may be supposed to be nonexistent, and it is such figures that are used in column 6 of table 2. Even if the size of fiber (i. e., here, degree of myelinization) is undergoing change as it approaches the periphery, it should be its condition as it approaches its end-organ which is significant if there is any significance; and in table 2 it is the proportion of large to small fibers (column 7) in the final sections of the unbranched nerves that is used.

(*b*) Results: It will be seen that in the case of the third nucleus there is found in this instance (columns 3 and 8) a fair correlation between the proportions of large and small fibers and large and small cells, although this is less striking in the case of the fourth and sixth nerves, even though the general trend here is in a similar direction.

It is interesting to note the 30 to 40 per cent excess of cells in the third and fourth nuclei over the number of fibers in the rootlets of the peripheral nerves, and the comparatively modest excess in the sixth.

TABLE 2.—*Correlation of Cells and Fibers in Central Nuclei and Peripheral Trunks*

	Number of Cells in Central Nuclei					Fibers		
			Proportion Large to Small	Excess Over Fibers			Relation Large to Small	Proportion Large to Small
	Large	Small		Number	% of the Total Cells	Number		
Derivation	Actual Count	Actual Count	1 : 2	(1+2)—6	4/(1+2)	Actual Count*	Actual Count†	From 7
Column no....	1	2	3	4	5	6	7	8
III normal....	4345	3004	1.44:1	2965	40	4384	3284:1909	1.54:1
degenerate	4249	2123	2.00:1	1988	31	(4384)	.....	(1.54:1)
IV right.....	628	480	1.30:1	491	44	617	652:277	2.36:1
left.....	442	445	1.00:1	267	30	620	.....	(2.36:1)
VI right.....	871	497	1.75:1	150	12	1209	964:343	2.80:1
left.....	1016	498	2.04:1	115	8	1399	655:917	0.72:1

* Central. † Peripheral.

Since the presence of "collaterals" from the median longitudinal fasciculus to the third and fourth nuclei is regularly described in textbooks, and since van der Schueren [17] experimentally demonstrated that the sixth nucleus in the rabbit does not harbor any cells of origin for this fasciculus, the cells might be assigned to "association" and the disposition on paper of their fibers to this bundle might be considered. The excess of cells, however, is not confined to any particular group and for the third nucleus alone totals nearly 5,000 cells, although the difference between intact and degenerated cells in this nucleus is only 973 (table 1). There is no reason to suppose that the usually slow secondary neuronal degeneration (reaction à distance) in association cells should take place in the seventeen days that elapsed. If the excess of cells were associatory and without peripheral fibers, they should not show degeneration at this stage; statistically there would then be a vast excess of intact cells—contrary to the observation (table 1). The excess is therefore

not ascribable to association cells resident in the nuclei but not sending fibers to the periphery. It is interesting in this connection to note that in dog C 8 the number of cells in the third and fourth nucleus complex is: right, 7,410; left, 7,378, as against right, 7,694, left, 7,894 in dog C 4. Neither Perlia's median nucleus nor Edinger-Westphal cells are included in these, or preceding, figures; nor, it will be noted, are Edinger-Westphal cells considered as having fibers in the peripheral trunks, for the purposes of this correlation.

The Central Afferent Cell.—It has already been shown (table 2) that there is rough correlation between the size of the fiber and that of the cell, Perlia's median nucleus with its relatively small number of cells (317) being disregarded; reasons for not considering any particular group of cells or excess of cells as associatory have just been given. Whether these small cells mediate kinesthetic sense is still a matter of conjecture; in this connection, however, Malone's recent statement [32] is pertinent; after recalling the efferent Nissl structure of the cells of those proprioceptive routes that send fibers to the cerebellum (i. e., Clarke's column cells are related to the efferent type; some cells of the nucleus gracilis and cuneatus; pontile nuclei; arcuate nuclei; inferior olive; lateral reticular nuclei; as well as the Purkinje cells and internal nuclei of the cerebellum), he says, "I believe that caudal to the diencephalon, sensory correlation is limited to the quadrigeminal plate, cerebellum, and certain exteroceptive (and probably visceral) reception centers; none of these centers are purely sensory, while the cerebellum is largely efferent. In my opinion the extent of the efferent mechanism for local correlation has been greatly underestimated. . . ."

The foregoing inference being granted temporarily, a possible experimental attack in this instance is suggested by Buzzard and Greenfield's [33] statement that, "The peripheral sensory neurons have been investigated in the same [Nissl] way. . . . Division of the peripheral or cellulipetal axons is generally followed by a . . . perinuclear chromolysis, enlargement of the cell body and lateral displacement of the nucleus. . . . The onset of these changes is detected in twenty-five to thirty hours after the nerve division, and reaches its height at the end of seven days. In the majority of cases the reaction is followed by repair, which, again, is of shorter duration than the corresponding stage in motor neurons." Although this statement does not specifically include cells within the cerebrospinal axis, it offers a possible method of attack by killing an animal six days after intracranial section of an extra-ocular nerve. In this connection it should be noted that chroma-

32. Malone (footnote 16, third reference).

33. Buzzard, E. F., and Greenfield, J. G.: Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1923.

tolysis has already been found much more advanced in the smaller cell type than in the larger (table 1, columns $\frac{20+24:21+25}{22+26:23+27} < 1$). The problem is being attacked further.

SUMMARY

1. The cells of the third, fourth and sixth nuclei of the dog can be separated into two distinct sizes, hitherto unrecognized, both having the "motor" type of tigroid substance, and being in general diffusely intermingled throughout the nuclei.

2. In the dog the proportions of these sizes correlate roughly with the sizes of fibers in the peripheral trunks, more especially in the case of the third cranial pair.

3. In the dog there is an excess of cells in the central nuclei of the extra-ocular muscles over the number of fibers in the central ends of the peripheral homologous trunks, roughly from 30 to 40 per cent for the third and fourth nerves, and 10 per cent for the sixth nerve.

4. Dichotomy of nerve fibers occurs distally within the peripheral trunks of the extra-ocular nerves of the dog.

5. Adequate peripheral cell nidi for the mediation of kinesthetic sense of the extra-ocular muscles of the dog have not been demonstrated.

6. It is suggested that the smaller cells described in the central nuclei of the dog mediate the kinesthetic sense of the extra-ocular muscles; incomplete evidence is considered, and possible modes of further attack are indicated.

NEUROLOGIC COMPLICATIONS ASSOCIATED WITH CONGENITAL STENOSIS OF THE ISTHMUS OF THE AORTA

A CASE OF CEREBRAL ANEURYSM WITH RUPTURE AND A CASE OF INTERMITTENT LAMENESS PRESUMABLY RELATED TO STENOSIS OF THE ISTHMUS *

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The remarkable anomaly of congenital stenosis of the isthmus of the aorta is replete with complications that involve the nervous system sufficiently often to command our attention. An idea of the incidence of this anomaly may be obtained by noting Fawcett's [1] review of 22,316 necropsy examinations conducted at Guy's Hospital between 1826 and 1902, in which he encountered stenosis of the isthmus eighteen times. A searching, although necessarily incomplete, review of the literature disclosed thirty-two cases in which some neurologic complication occurred. This group represents about 7 per cent of the reported cases of stenosis of the isthmus.[2]

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* From the Section on Neurology, Mayo Clinic.

* Read at the Fifty-Second Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 1-3, 1926.

1. Fawcett, J.: Coarctation of the Aorta, as Illustrated by Cases from the Postmortem Records of Guy's Hospital from 1826 to 1902, Guy's Hosp. Rep. **59**:1-19, 1905.

2. Gossage, A.: Case of Coarctation of the Aorta, Proc. Roy. Soc. Med. **6**:1-5, 1912-1913. Goodhart, J. F.: Coarctation of the Aorta Below the Left Subclavian, Tr. Path. Soc. **26**:68-74, 1875. Bonnet, L. M.: Sur la lésion dite sténose congénitale de l'aorte dans la région de l'isthmus, Rev. de méd. **23**:108, 255, 335, 418 and 481, 1903. Erman, F.: Ein Fall von angeborene Stenose der Aorta an der Einsenkungstelle des Ductus Botalli, Berl. klin. Wchnschr. **10**:217-221, 1873. Focken, E.: Isthmus Stenose und Endocarditis, Ztschr. f. klin. Med. **100**:179-189 (May) 1924. Huchard, H.: Le pouls anacrote dans le rétréssisment aortique, Bull. et mém. Soc. méd. d. hôp. de Paris **13**:364-369, 1896. Laboulbéne, A., and Claisse, R.: Rétréssisment congenital aortique, Bull. et mém. Soc. méd. d. hôp. de Paris **7**:945-947, 1890. Manneberg, I.: Ueber die Stenose und Obliteration der Aorta in der Gegend der Insertion des Ductus arteriosus Botalli, Inaug. Dissert., Breslau, 1884. Mercier, A.: Rétréssisment aortique avec oblitération presque complète de la portion thoracique de l'aorte, Bull. Soc. anat. de Paris **14**:158-160, 1839. Muriel, W.: A Case of Contracted Aorta, Guy's Hosp. Rep. **7**:443, 1842; Arch. gén. de méd. **15**:349, 1842. Osler, E.: An Account of Sir Astley Cooper's Case of Ligature of the Abdominal Aorta, July 5, 1817;

ANATOMIC CONSIDERATIONS

A discussion of this anomaly from embryologic, anatomic and semiologic standpoints, while interesting, has been presented ably many times and it is not necessary here. The site of stenosis of the isthmus in the adult is almost invariably proximal to the junction of the ligamentum arteriosum with the aorta. The stenosis may be complete but is said to exist when the lumen of the aorta is constricted locally in excess of 3 mm.

The cause of the deformity is doubtful. Traction exerted by the fibrosing ductus, thrombosis, endarteritis extending from the ductus into the aorta, and misplaced rests of the ductus in the aortic walls are among the suggested causes.

CLINICAL CONSIDERATIONS

The presence or absence of symptoms depends not so much on the degree of stenosis as it does on the development of an adequate collateral circulation. The vessels through which this takes place (fig. 1) are chiefly derived from the arteria subclavia, the transversa scapulae, the intercostalis suprema and the transversa colli, which anastomose at least in part with the intercostales, thus shunting the blood to the aorta below the site of the stricture, and through the mammaria interna which anastomoses with the arteria epigastrica, by this route conveying blood to the hypogastrica and iliaca externa. This situation leads to the development of the cardinal signs of congenital stenosis of the isthmus. They are: (1) A discrepancy in the pulsation of the arteries below the site of the stenosis as compared with that above. The pulse in the dorsalis pedis, the tibialis posterior, the femoralis and the aorta may be impalpable or feeble, and may present a slow accent and delay in reaching the apex [3] or an ascending and descending dicrotism, best determined by sphygmographic methods; the pulsation of the subclavia and carotis communis, on the other hand, is usually excessively strong. (2) In about one fourth of the cases [4] enlarged, tortuous and strongly pulsating anastomosing arteries may be demonstrated over the upper part of the

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Guy's Hosp. Gaz. **31**:875, 1917. O'Flaherty, H.: Ein Fall von Stenocardie und Strictur der Aorta, Berlin, Canstatt's Jahresbericht, 1868, vol. 2, p. 71. Reynaud, A.: Observation d'une oblitération presque compléte de l'aorte, J. hebd. de méd. **1**:161-175, 1828. Scheele: Ein Fall von Stenose des Isthmus Aortae, Berl. klin. Wchnschr. **7**:32-36, 1870. Weber, F., and Price, F.: Coarctation of the Aorta in an Adult with Death due to Rupture of an Aneurysm in the Neck, Lancet **2**: 692, 1912.

3. Stursberg, H.: Sphygmographe Befunde bei Verengerung der Aorta am Isthmus, Deutsches Arch. f. klin. Med. **107**:33-38, 1912.

4. Barié, E.: Oblitération de l'aorte abdominale et des artères iliaques primitives par un caillot; paraplegie subite, Bull. Soc. anat. de Paris **1**:22-26, 1876; Progrès méd. **4**:296, 1876; Du rétrecissément congénital de l'aorte descendante, Rev. de méd. **6**:343, 409 and 501, 1886.

chest. (3) Evidence of cardiac overload and a break in compensation often occur. Any one or all of these signs may be absent.

The result of the anomaly is essentially an oversupply of blood to the upper part of the body and a deficient supply to the lower part. The former condition more commonly leads to serious results. Death is usually due to rupture of an aneurysm of the proximal part of the aorta (12 per cent [5]), cerebral accidents and cardiac decompensation.

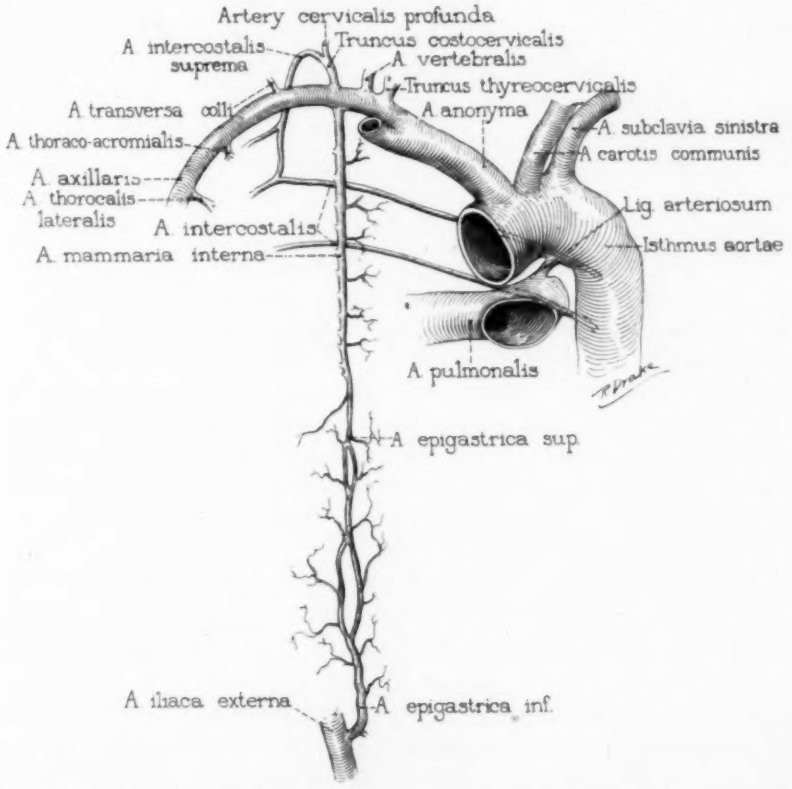

Fig. 1.—Schematic drawing of the larger vessels to illustrate some of the anastomotic channels developed in the stenosis of the isthmus.

The average age at death is given by Martens as 34, and by Meixner [6] as a trifle more than 30. In the group of thirty-two cases, the mean age at death was about 27. The oldest patient died from a cerebral hemorrhage after reaching the age of 92. Stenosis of the isthmus has often been found unexpectedly at necropsy.

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5. Sella, H.: Aortenruptur und Aortinaneurysma bei Aortinstenose am Isthmus, Beitr. z. path. Anat. u. z. allg. Pathol. **49**:501-528, 1910.

6. Meixner, K.: Berstung der aufsteigenden Körperschlagader bei Verschluss am Ende des Bogens, Beitr. z. gerichtl. Med., 1922, pp. 72-90.

NEUROLOGIC ASPECTS

General Manifestations.—Neurologic complications, while not infrequent, have rarely called forth comment. Nowhere, to my knowledge, has the subject been dealt with from this aspect. Sommerbrodt[7] made the statement that changes in the brain would be found more often if complete necropsy was performed. The following neurologic complications were encountered in the entire series: headache (44 per cent); hemiplegia (34 per cent); convulsions (19 per cent); rapid fatigue and a sensation of cold in the lower extremities (19 per cent); vertigo (12.5 per cent); tinnitus (9.4 per cent), which in one patient was so marked that it interfered with sleep; transitory disturbances of the field of vision, edema of the disks and mental deterioration. At necropsy, cerebral hemorrhage was encountered in 37.5 per cent, softening in 19 per cent, aneurysm with rupture in 9.4 per cent and embolism in 6.2 per cent.

Three cases have been reported in which stenosis of the isthmus was associated with an aneurysm of a cerebral artery that had ruptured with fatal results. Eppinger,[8] in 1871, reported the case of a boy, aged 15, who was unusually active in gymnastics. He had frequently complained of precordial pressure and congestion in the head. Three days before death he collapsed suddenly. Necropsy disclosed transposition of the large vessels of the neck, cardiac hypertrophy, stenosis of the isthmus to the size of a bristle, congested meninges, free blood at the base of the frontal lobes and aneurysms of both anterior cerebral arteries, with rupture of the right one.

Kolisko,[9] in 1913, reported the case of a man, aged 26, who had recovered from an attack of insanity a few years previously. After a hard day's work he suddenly developed headache, vomited and died. At necropsy were found complete stenosis of the aorta at the isthmus, cardiac hypertrophy, a well developed collateral circulation and an aneurysm of the anterior communicating artery, about 1 mm. in diameter, which had ruptured and caused extensive hemorrhage over the base.

The third case was reported by Strassmann,[10] in 1922. The patient was a boy, aged 13, who fell forward dead while playing football. Necropsy disclosed cardiac hypertrophy, stenosis to about 1 cm. at the

7. Sommerbrodt, M.: Typischer Fall von Obliteration der Aorta thoracica in der Gegend der Einmündungstelle des Ductus arteriosus, Arch. f. path. Anat. **91**:492-499, 1883.

8. Eppinger, A.: Stenosis Aortae congenita seu Isthmus persistens, Vrtljschr. f. d. prakt. Heilk. **112**:31-67, 1871.

9. Kolisko, A.: Plötzlicher Tod aus natürlicher Ursache, Handbuch d. ärtzl. Sachverständigentätigkeit, Vienna and Leipzig, Braumüller, 1913, p. 984.

10. Strassmann: Der plötzliche Tod bei Stenose des Isthmus Aortae, Beitr. z. gerichtl. Med., 1922, pp. 91-97.

isthmus, and an aneurysm of the sylvian artery near its origin from the internal carotid which had ruptured and caused extensive bleeding over the base and cortex. It will be noted that all of these patients were young, robust, vigorous males, and that rupture of the aneurysm was evidently the immediate result of physical strain.

In six cases, the cause of death was cerebral hemorrhage, although no aneurysm was present.

De Almagro,[11] in 1862, reported the case of a girl, aged 19. Since the age of 3, it had been noted that whenever she cried the arms became cyanotic; at the age of 5, palpitation and dyspnea appeared, and at 10 she developed epistaxis. At 19, she was suddenly stricken with vertigo, and manifested left motor and sensory hemiplegia. Death occurred a few hours later. At necropsy, tubercles were found in the left lung; there were cardiac hypertrophy, stenosis of the isthmus, and in the right striate body a chocolate colored spot, 4 by 3 cm., associated with softening.

Kriegk,[12] in 1878, reported the cases of two patients who died from cerebral hemorrhage. The first, a boy, aged 11, was markedly precocious in mental development. Two years previously he had complained of pain in the galea which lasted three days. About ten days before death he fell and struck his head, and three days later complained of severe headache which resembled the original pain in the galea. He became gradually stuporous. Examination disclosed cardiac hypertrophy, rigidity of the neck, slight ptosis on the right and hyperemia of the disks. Left hemiplegia developed, and the patient died during a convulsion. At necropsy, left ventricular hypertrophy, absence of one semilunar valve, a patent foramen ovale, stenosis of the isthmus to the size of a bristle and hemorrhage into the right parietal lobe and superficially near the sylvian fissure were found.

The other case was that of a woman, aged 28, in the seventh month of pregnancy, who had complained of dyspnea on exertion during the previous seven years. While putting her child to bed she experienced palpitation, precordial pressure, vertigo and twitching of the right side of the body. Right hemiplegia developed, and she lost consciousness. Examination disclosed right motor and sensory hemiplegia. Cardiac embarrassment became severe. The patient suffered another stroke and died. At necropsy the heart was found to be hypertrophied, and there were nephritis, stenosis of the isthmus to about 2 cm., a hemorrhage into the right hemisphere with rupture into the right ventricle, and an

11. De Almagro, M.: Étude clinique et anatomo-pathologique sur la persistance due canal artériel, Thése Paris, no. 63, 1862, pp. 120.

12. Kriegk, M.: Drei neue Fälle von Stenose der Aorta in der Gegend der Insertion des Ductus Botalli, Vrtljschr. f. d. prakt. Heilk. **137**:47, 1878.

area of softening in the left operculum. Kriegk believed that both the nephritis and the stenosis contributed to the fatal outcome.

Sommerbrodt, in 1883, reported the case of a patient, aged 46, who had suffered from palpitation since childhood. He had complained of weakness of the legs for a long time. Twelve years previously, he had had several attacks of hemiplegia. Dysphagia, dysarthria and progressive dementia were present. On examination, there were noted left facial hemihypertrophy, dilatation of the vessels of the face, enlargement of the arteries over the back of the chest and almost complete absence of pulsation of the crural vessels. Necropsy disclosed dilatation of the epigastric arteries, cardiac hypertrophy, complete closure of the aorta at the isthmus, sclerosis of the vessels of the base of the brain, an aneurysm of the left vertebral artery 2 cm. from the basilar artery and multiple areas of softening in the brain. The ependymal surface of the fourth ventricle was stained brown as if from a previous hemorrhage.

Moon,[13] in 1912, reported the case of a patient, aged 17, who had had Bell's palsy twice. Since childhood he had frequently complained of dyspnea. The legs were unusually feeble. Two weeks before death, the left arm and side of the face became paralyzed. One and one-half hours before death he developed right hemiplegia with loss of speech. The blood pressure was 180 mm. The femoral pulse was scarcely perceptible. At necropsy, the abdominal aorta and iliac arteries were found to be unusually small; there was stenosis of the aorta at the isthmus, and recent slight subcortical hemorrhage in the right postrolandic area.

Follet and Caille,[14] in 1921, reported the case of a boy, aged 17, who had fallen from a horse seven weeks before death, producing slight abrasions about the scalp. The fall was attributed to hypertension. Two weeks before death, while lifting some heavy sacks of grain, he fell without loss of consciousness and assumed the posture seen in meningitis. Examination disclosed cardiac hypertrophy, a precordial bruit, a pulse rate of 50, dilated, tortuous arteries over the anterior and posterior aspects of the thorax and absence of femoral pulse. Friction above the umbilicus produced a red line, below it a white line. The Babinski reflexes were positive. The spinal fluid was bloody. The patient died fifteen days later. At necropsy, cardiac hypertrophy, extensive collateral circulation, a filiform stricture at the aortic isthmus and extensive hemorrhage at the base of the brain were noted.

REPORT OF CASES

CASE 1.—A strong, active boy, aged 20, whose only complaint had been occasional attacks of dizziness, was registered at the Mayo Clinic, May 3, 1925. Five weeks before he had pushed a motorcycle through a mile of sand, had

13. Moon, R. A.: Congenital Stenosis of the Aorta, Lancet **1**:1531, 1912.

14. Follet and Caille, E.: Sur un cas de sténose totale de l'aorte thoracique, Arch. d. mal. du coeur **14**:207-211 (May) 1921.

called at a farmhouse for some fuel and, while chatting with the proprietor, had suddenly fallen to the ground for no apparent reason. He immediately regained his feet and rode to his home. During the subsequent week he pursued his usual activities but experienced a sensation of pressure in the head. Two weeks before admission, while playing ball, he was stricken with a severe pain in the occiput; he became dizzy, broke out in a cold sweat, staggered through the house and was helped to bed. Subsequently he vomited a number of times and manifested marked photophobia and restlessness. Two days before entering the hospital, he suddenly sat up and screamed because of severe pain in the back of the neck. He said that his neck was broken and that he was going to die. Morphine, ¼ grain (0.016 Gm.), was administered, and following this he became unconscious. In this condition he reached the clinic.

There was generalized rigidity, and the limbs jerked occasionally. The Hoffmann and Babinski reflexes were strongly positive. The pupils reacted to light, but the left was slightly larger than the right. There was mild edema of the optic disks; the arteries were slightly contracted and the veins slightly dilated, and there were several massive hemorrhages of both retinas and disks and the right macula. The cardiac dulness was 3 by 11.5 cm.; a palpable thrill was noted over the aortic area and carotid vessels. The pulse rate varied from 50 to 60. The systolic blood pressure in the right arm was 164 and the diastolic 86; in the left the systolic was 126 and the diastolic 110; in the legs a few slight oscillations were noted, between 80 and 90 mm. The right carotid artery crossed from the left to the right in the suprasternal notch. Compression of the strongly pulsating left carotid artery stopped the left radial pulse. The left subclavian artery could not be palpated. A small artery descended from the left mastoid region toward the outer end of the left clavicle. Compression of this vessel diminished the volume of the left radial pulse. Two moderately large arteries could be palpated between the vertebral column and the border of each scapula, and several large, tortuous, strongly pulsating arteries were palpable in the right posterior axillary line. The abdominal aorta was not palpable. A slight pulsation was noted in the right femoral artery. The leukocyte count was 11,800. The spinal fluid was moderately bloody. Other physical and laboratory observations were essentially unimportant.

On the fourth day after admission the patient appeared brighter, was less restless and talked rationally, but on the following day he again lapsed into unconsciousness. The pupils were dilated; reaction to light was diminished and left ptosis appeared. On the sixth day after admission he became very restless, but it was noted that he did not move the right arm or leg, and the right half of the face seemed somewhat weak. He did not talk. The left pupil became large and fixed; the right was normal in size but reacted only slightly to light. The choking of the disks had increased to 3 diopters. Twice during the night respiration ceased, and cyanosis appeared, lasting one and one-half minutes. Before death, which occurred May 12, the pulse rose to 180, the temperature to 104.6. While he was in the hospital, there had been daily fluctuations of temperature, usually with a rise to 104.

A diagnosis was made of congenital stenosis of the isthmus of the aorta, developmental anomalies of the vessels of the neck and cerebral hemorrhage.

Necropsy was performed the morning after death. The pericardial cavity had a transverse diameter of 11 cm. and contained 10 cc. of clear, straw-colored fluid. The heart was hypertrophied. The aorta, which was slightly sclerotic, was normal in size up to the origin of the arteria anonyma; beyond this point it rapidly narrowed and ended blindly (fig. 2) at the point of origin of the subclavia sinistra. The ductus arteriosus was closed and about 1 cm. in length. Beyond

the point of occlusion, the aorta enlarged slightly, but remained small throughout the remainder of its course. The orifices of the intercostales were larger than normal, as were the vessels themselves. The carotis communis sinistra took origin from the aorta in the usual manner. The first part of the subclavia sinistra was represented by a firm cord, from 2 to 3 mm. in diameter, which maintained the usual relations of this vessel. The second part, continuous with the occluded cord, began abruptly with a bulbous enlargement 1 cm. in diameter. This dilated portion was 2 cm. in length, beyond which the vessel became narrower and continued as the second and third parts of the subclavia. The usual series of vessels left it, but the truncus thyreocervicalis, the arteria mammaria interna and the transversa colli were larger than normal. The cervical and scapular groups of vessels and the occipitalis and auricularis posterior evidently supplied most of the

Fig. 2.—Anterior view of heart and great vessels, showing the stenosis of the aorta just below the insertion of the ligamentum arteriosum and the fibrotic band representing the first part of the arteria subclavia sinistra.

blood that entered the distal two thirds of the subclavia sinistra by way of devious and widespread anastomoses, thus supplying the arms with blood.

The arteria anonyma divided into the usual branches. The right truncus thyreocervicalis, the arteria vertebralis and its branches, and the thoracalis lateralis were greatly enlarged. The right mammaria interna was three times its normal size and larger than its fellow of the opposite side. The truncus costocervicalis dextra went almost entirely to form a large arteria intercostalis suprema (fig. 3) which, through an anastomotic vessel of large caliber, entered the greatly dilated intercostalis of the third interspace, through which blood ran into the aorta contrary to the usual direction. Through these devious communications, a large volume of blood was shunted past the stricture into the distal thoracic aorta.

The kidneys presented fetal lobulations. The spleen and liver were congested. There was terminal bronchopneumonia.

When the dura was reflected, a slight amount of blood was noted over the convexity. When the brain was removed from its cavity, a large collection of blood was found covering the base. The arteria carotis and the arteria vertebralis were larger on the right than on the left. At the juncture of the left communicans posterior with the cerebri media, a dumbbell-shaped aneurysm (fig. 4) extended backward and under the nervus oculomotorius, which was raised from its bed and stretched over it. This aneurysm had ruptured and was responsible for the free blood found. At the juncture of the communicans anterior with the right cerebri anterior was a smaller aneurysm, about 4 mm. in diameter.

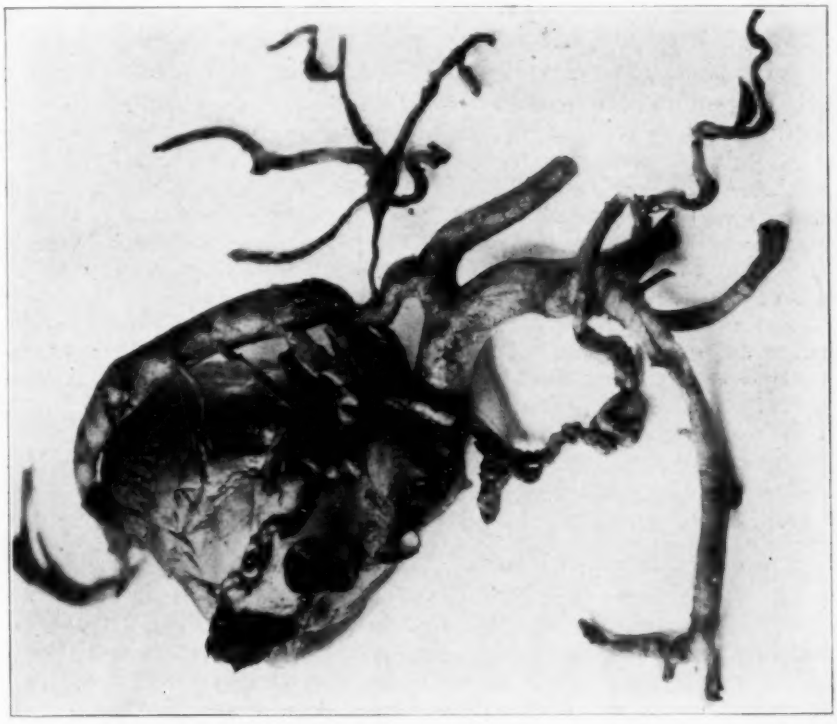

Fig. 3.—Posterior view of heart and vessels, showing the greatly enlarged and tortuous arteria intercostalis suprema.

Disturbances Noted in the Lower Extremities.—Since Charcot's portrayal of intermittent claudication in man, this syndrome has become universally familiar. It is usually associated with some disease obliterating the vessels of the limbs. Functional disturbances of the lower extremities have also been reported with obstruction of the aorta by embolism, as described by Jean,[15] Nocard[16] and Barie, thrombosis,[17]

15. Jean, A.: Oblitération de l'aorte par un caillot; claudication intermittente, puis paraplégie, Bull. Soc. anat. de Paris **10**:232-235, 1875.

aortitis,[18] and ligation, as described by Cooper, Milton,[19] Keen,[20] Halsted [21] and Vaughan.[22] Compression of the pulsating aorta by extrinsic disease processes is rare. Velpeau [23] described a case of aortic obstruction due to cancer. The changes that take place in the cord following obstruction of the aorta have been described by Rothmann,[24] Alexander and others. Whether the disturbances noted in the lower extremities are due to the changes in the cord or result from a relative ischemia of the peripheral muscles and nerves remains a disputed question. Alexander believed that both factors may play a part.

We are justified in inquiring whether the collateral circulation to the lower limbs in cases of stenosis of the isthmus is always sufficient to insure satisfactory function. Evidently it is not. Lebert's [25] patient for five years complained of pain in the calves and swelling of the feet on walking and standing. Redenbacher,[26] in 1873, in describing the case of his son, said that he was overdeveloped above, but that the legs were weak; he

16. Nocard: Boiterie intermittente causée par l'obstruction partielle de l'aorte posterrieure, France méd. **22**:218-220, 1875.

17. Barth, M.: Observation d'une oblitération de l'aorte abdominale, Arch. gén. de méd. **8**:26-52, 1835. Gull, W.: Case of Paraplegia from Obstruction of the Abdominal Aorta, Guy's Hosp. Rep. **3**:311-314, 1857. Jourand: Thrombose et oblitération de l'aorte thoracique; parésie de membres inférieurs, à deux reprises differentes; athérome généralisée trés prononcé aux coronaires; hypertrophie et dilatation du coeur; dégenéréscence granulograisseuse de la fibre cardiaque; accidents asystoliques, Bull. Soc. anat. de Paris **56**:466-470, 1881. Alexander, A.: Zur Kenntniss der Rückenmarksveränderungen nach Verschluss der abdominalen Aorta, Ztschr. f. klin. Med. **58**:247-261, 1905-1906. Cattle, C.: Occlusion of the Abdominal Aorta, Lancet **1**:1691, 1908.

18. Clerc, A., and Clarac, G.: Oblitération de l'aorte abdominale avec aortite chronique, Bull. et mém. Soc. méd. d. hôp de Paris **35**:1084-1091, 1913.

19. Milton, N.: Ligature of the Abdominal Aorta for Ruptured Aneurysm of That Vessel, Lancet **1**:85, 1891.

20. Keen, W.: A Case of Ligature of the Abdominal Aorta Just Below the Diaphragm, the Patient Surving for Forty-Eight Days; with a Proposed Instrument for the Treatment of Aneurysm of the Abdominal Aorta by Temporary Compression, Am. J. M. Sc. **120**:251-277, 1900.

21. Halsted, W. S.: Partial, Progressive and Complete Occlusion of the Aorta and Other Larger Arteries in the Dog by Means of the Metal Band, J. Exper. Med. **11**:373-391, 1909; Proc. Soc. Exper. Biol. and Med. **10**:113-116, 1912-1913.

22. Vaughan, G. T.: Ligation of the Aorta: Necropsy Two Years after Operation, Ann. Surg. **76**:519 (Oct.) 1922.

23. Velpeau, A.: Cas remarquable de maladie cancéreuse, avec oblitération de l'aorte, Ann. de l. méd. Physiol. **7**:232-249, 1825.

24. Rothmann, M.: Ueber Rückenmarksveränderungen nach Abklemmung der Aorta abdominalis beim Hunde, Berl. klin. Wchnschr. **36**:575, 1899.

25. Lebert, H.: Ueber die Verengerung der Aorta in der Gegend des Ductus arteriosus, Arch. f. path. Anat. **4**:327-374, 1851.

26. Redenbacher, W.: Verengung der Aorta descendens an der Insertionstelle der Aorta durch Endocarditis, Polyarthritis synovialis embolica, Bayer. ärztl. Intell.-Bl. **20**:97-103, 1873.

stumbled easily and almost every night fussed about for several hours because his legs refused to warm up. A patient of Sommerbrodt, in 1883, and one of Leyden,[27] in 1889, both had had weakness of the legs for a long time. Moon, in 1912, said that: "The symptoms of intermittent claudication, which a priori one might expect to find, are said always to be absent, even in most extreme degree of constriction, thus indicating that the blood supply to the lower limbs is physiologically sufficient; but in my case the patient was said to have been always weak on his legs, which would suggest that the collateral circulation in the lower limbs was not sufficient." Edelmann and Maron,[28] in 1922, thought

Fig. 4.—Base of brain showing aneurysm at the juncture of the left arteria communicans posterior with the cerebri media, the injured left nervus oculomotorius (raised with a probe) and the aneurysm at the juncture of the arteria communicans anterior with the right cerebri anterior.

that milder subjective disturbances may occur. Their patient complained of an ice-cold sensation of the feet.

Leyden reported the case of a patient who complained among other things of impairment of function in the legs on exertion. Necropsy disclosed a congenitally small arterial system. In this developmental anomaly, first described by Virchow, the vessels are uniformly hypo-

27. Leyden, E.: Angeborene Enge der Aorta, Charité-Ann. **14**:151-157, 1889.

28. Edelmann, A., and Maron, R.: Die Isthmus Stenose der Aorta und ihre differential Diagnose, Wien. Arch. f. inn. Med. **4**:1-10 (April) 1922.

plastic, which is not the case in the patients under consideration; however, it does have a bearing on our subject.

We could find only one case report in which a frank diagnosis of intermittent claudication based on a congenital stenosis of the aorta was made. This was supplied by Fröhner,[29] a veterinarian. The history and physical examination of a horse, aged 8 years, would have satisfied the most punctilious internist, had he not neglected a careful chemical study of the blood. This horse, which Fröhner used for teaching purposes, had had symptoms of intermittent claudication since birth. Necropsy verified his diagnosis.

The syndrome of intermittent limping in the following case, we believe, was the result of a congenital stenosis of the aortic isthmus, although that opinion was not confirmed by necropsy:

CASE 2.—A woman, aged 44, had registered at the Mayo Clinic on several occasions, the last time, Jan. 16, 1925. In 1910, while traveling in India, she became subject to sudden, recurrent attacks of loss of consciousness which usually came on while mountain climbing. The duration of these lapses was an hour or less, and they were followed by a sense of precordial pressure. There were no convulsions. One afternoon while walking strenuously in the blazing sun, she was overcome in a similar manner. This time convalescence required two months. Examination showed that the heart was dilated well into the axillary line. Following this, she enjoyed excellent health with the exception of two syncopal attacks, one in 1920 and the other in 1924. She attributed these to heat and exertion.

In 1923, sixteen months before we saw her, the patient began to experience a sensation of heaviness in the sacral region after walking about three blocks; the upper parts of the thighs seemed to push through the pelvis into the body; the feet became numb, the calves cramped and further progress seemed impossible. A rest of two or three minutes would relieve the situation so that she could again proceed, after which the same series of disturbances recurred. Should she persist in repeating this performance with too much vigor, a sensation of precordial pressure, dyspnea, tachycardia, vertigo and occasional vomiting would appear. Recovery would then require several hours. These sensations, always brought on by exertion, had become daily experiences for sixteen months.

The patient was well developed, well nourished, apparently healthy, intelligent, and free from any obvious psychoneurotic manifestations. The general and neurologic examinations and routine laboratory tests gave essentially negative results with certain exceptions. There was slight tenderness over both sacro-iliac joints, and the roentgen ray disclosed slight sacro-iliac hypertrophic arthritis. The heart was dilated 5 cm. toward the left; the first sound at the apex was occasionally roughened. The electrocardiogram showed nothing of consequence. The systolic blood pressure taken on the arm was 150 and the diastolic 84. No dilated arteries were visible or palpable over the chest wall. Pulsation in the subclavian arteries was prominent and strong. No pulsation could be palpated over the dorsalis pedis, posterior tibial and iliac arteries, and none over the abdominal aorta. A faint bruit was occasionally audible on deep pressure with

29. Fröhner: Angeborene Aortenstenose als Ursache des intermittierenden Hinkens, Monatschr. f. prakt. Tierh., Stuttg. **16**:553-558, 1905.

the stethoscope in the epigastric region. When the cuff was placed around the lower portion of the thigh, the oscillation of the needle of the tycos sphygmomanometer was barely perceptible at a pressure of 100 mm. No sound could be heard.

Although the diagnosis of congenital stenosis of the isthmus in this patient has not been verified by necropsy, the excessive pulsation in the subclavian arteries, the absence of a palpable pulse in the abdominal aorta and arteries of the lower extremities, the hypertension in the upper limbs, the hypotension in the lower limbs and the cardiac symptoms and signs sufficed to establish a presumptive diagnosis of this anomaly. To be sure, other conditions such as tumor and thrombosis may occasionally result in obstruction of the aorta, yet we have no reason for assuming the presence of such decidedly rare possibilities in face of the relatively frequent anomaly of stenosis of the isthmus. A history of cardiac decompensation on exertion is common and readily understood. The syncopal attacks noted in this patient are not so easily explained. They may have a circulatory basis, for we see them frequently in cases of paroxysmal tachycardia. As already noted, convulsions were present in six of the thirty-two cases gathered from the literature.

The disturbance of function in the lower portion of the trunk and in the lower extremities must at once suggest intermittent claudication. The resemblance of this patient's complaints to the syndrome described by Hunt [30] as ischemic lumbago, or the lumbar type of intermittent claudication, is striking. Hunt explained this condition by assuming a disease of one or more of the lumbar arteries which rise from the aorta or arteriosclerosis of the aorta itself. In his cases, however, he mentioned pulsation of the aorta and femoral arteries. In our case and in Hunt's cases, muscular ischemia must probably be assumed. There were no signs, such as impairment of sphincters or involvement of the pyramidal tract, that would suggest the syndrome of intermittent claudication of the cord to which Dejerine [31] called attention.

SUMMARY

The subject of the neurologic complications associated with stenosis of the isthmus may be summarized somewhat categorically. Experience has taught us that in the congenital anomaly of stenosis of the isthmus, circulatory disturbances may arise which are often of interest to the

30. Hunt, J. R.: The Lumbar Type of Intermittent Claudication, Am. J. M. Sc. **143**:173-177, 1912; Unilateral Intermittent Claudication of the Lumbar Region, J. Nerv. & Ment. Dis. **40**:123-125, 1913; Ischemic Lumbago: A Further Contribution to the Lumbar Type of Intermittent Claudication, J. A. M. A. **62**: 671-674 (Feb. 28) 1914.

31. Dejerine, J.: La claudication intermittente de la moelle épinière, Clinique Paris **6**:515, 1911; Presse méd. **19**:981-984, 1911; La claudication intermittente de la moelle épinière, Clinique, Paris **26**:506-514, 1912.

neurologist. Above the site of stenosis, the volume and pressure of blood may be excessive; this may result in cerebral disturbances and may be associated with, or contribute to the production of, aneurysms of the cerebral vessels which may rupture, with fatal results. This was obviously what occurred in case 1. In the lower extremities, the supply of blood may in rare instances be deficient. This may presumably bring about the syndrome of intermittent limping and is the explanation offered for the disturbance in case 2.

Congenital stenosis of the isthmus is no longer regarded as being excessively rare. Its recognition may be of interest and may even have the virtue of some practical value.

DISCUSSION

Dr. Chas. Bagley, Jr., Baltimore: Recently we have had some interesting experiences with cerebral aneurysms, and I should like to show some slides of one of the recent cases which came to necropsy.

A girl, aged 11, with no history of previous illness, on Jan. 31, 1926, was seized with a severe headache followed immediately by several convulsions. Lumbar puncture revealed bloody cerebrospinal fluid. The symptoms gradually improved over a period of two weeks. One month after the first attack, she had a second seizure and was admitted to the hospital. The condition at the time of admission was grave because of marked disturbance of the cardiorespiratory functions. There was a high grade choked disk, and the cerebrospinal fluid was again bloody. When question about a bruit, she stated that she had been hearing a noise for some time. On auscultation a loud bruit was heard over the entire head. Death occurred soon after admission, and necropsy revealed a large amount of blood in the ventricle and subarachnoid space, with a well organized clot as well as recent extravasation of blood near the anterior cerebral arteries. The slides were taken from this region of the brain and show a well laminated aneurysmal sac which had ruptured.

The case is presented as one of congenital aneurysm of the anterior cerebral artery, not associated with syphilis.

THE NATURE OF THE CEREBROSPINAL FLUID*

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The cerebrospinal fluid, noted by Galen, Vesalius and Valsalva, received its first important description from François Magendie,[1] in 1825. His monograph,[2] published in 1842, marked the beginning of numerous investigations stimulated by the increasing diagnostic and therapeutic importance of this fluid and its intimate relation to the problem of intracranial pressure.

Faivre,[3] in 1854, suggested that the choroid plexus was the source of the fluid, a view that has been accepted by most of the important investigators in this field; but it was not until 1919 that conclusive evidence was available. In that year, Dandy [4] demonstrated that obstruction of the foramen of Monro resulted in dilatation of the obstructed ventricle, but that such hydrocephalus never occurred if the choroid plexus of the same ventricle was removed.

Hassin,[5] however, seriously opposes the view that the choroid plexus is a source of cerebrospinal fluid. He believes that its chief function, like that of the arachnoid villi, is absorption. The following [6] is an example of the type of evidence, derived from pathologic studies, that he offers to support his contention: A case of carcinoma of the breast showed diffuse carcinomatosis of the meninges and a mass of carcinoma cells in the choroid plexus. Hassin states that the tumor cells reached the meninges by direct extension along the lymphatics of the neck, but unfortunately gives no evidence to prove this point so vital to his theory. He believes that the presence of tumor cells in the choroid plexus indicates that cerebrospinal fluid flows from the subarachnoid space into

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* Read at a Meeting of the Boston Society of Psychiatry and Neurology, Feb. 18, 1926.

1. Magendie, François: J. de physiol. expér. **5**:27, 1825.

2. Magendie, François: Récherches physiologique et clinique sur le liquide céphalo-rachidien, Paris, 1842.

3. Faivre, E.: Compt. rend. Acad. d. sc. **34**:424, 1854.

4. Dandy, W. E.: Tr. Am. Surg. A. **37**:397, 1919.

5. Hassin, G. B.: Histopathologic Findings in a Case of Superior and Inferior Poliencephalitis, Arch. Neurol. & Psychiat. **5**:552 (May) 1921; J. Nerv. & Ment. Dis. **59**:113, 1924; Effect of Organic Brain and Spinal Cord Changes on Subarachnoid Space, Choroid Plexus and Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **14**:468 (Oct.) 1925.

6. Hassin (footnote 5, third reference).

the ventricles and is absorbed by the choroid plexus. Since it is well known that carcinoma of the breast may metastasize by way of the blood stream as well as by way of the lymphatics, it appears that Hassin's original assumption, that invasion of the subarachnoid space occurred solely "through the lymph glands of the neck," is not justified. An exactly opposite interpretation of his observations of microscopic changes can be offered; namely, that a blood borne metastasis, either passing through the lung or arising from a metastasis in the lung (no report of the lungs is furnished in Hassin's paper) reached the choroid plexus, from which tumor cells escaped into the ventricle and thence were distributed throughout the subarachnoid space. Deductions based on pigments, admittedly of unknown nature, found within the cells of the choroid plexus, and on lipoids covering these cells are equally uncertain. This evidence, open to more than one interpretation, cannot stand against the crucial experiments of Weed [7] or Dandy.[4] It should be noted that the foregoing interpretation in no way invalidates the theory that the perivascular spaces pour their contents into both the subarachnoid space and the ventricles, thus contributing a small portion of the cerebrospinal fluid, a concept to which Hassin's researches have added valuable evidence.

ABSORPTION OF THE CEREBROSPINAL FLUID

The absorption of the cerebrospinal fluid through the pacchionian granulations into the cerebral venous sinuses was indicated by Key and Retzius [8] in 1870, and their observations were confirmed by Quincke [9] in 1872. The contributions of Key and Retzius,[10] Leonard Hill [11] and Cushing [12] culminated in the researches of Weed [13] in 1914, who injected isotonic nontoxic potassium ferrocyanide and iron and ammonium citrate into the subarachnoid space, under physiologic pressures. After allowing time for circulation of the fluid, he killed the animal and immediately fixed the brain and its coverings in acid solution. The acid caused the precipitation of Prussian blue granules wherever the injected solution had been carried. Thus he was able to follow the circulation of the fluid. He found that nearly all the Prussian blue granules were precipitated in the arachnoid villi, particularly along the superior longitudinal sinus and the cavernous sinuses, where the granules could be

7. Weed, L. H.: Physiol. Rev. **2**:171 (April) 1922.

8. Key, G., and Retzius, A., cited by Quincke (footnote 9).

9. Quincke, H.: Arch. f. Anat. u. Physiol. (Du Bois Reymond), 1872, p. 153.

10. Key, G., and Retzius, A.: Studien in der Anat. des Nervensyst. u. des Bindesgewebes, Stockholm, 1875-1876.

11. Hill, Leonard: The Cerebral Circulation, London, J. & A. Churchill, 1896.

12. Cushing, Harvey: Am. J. M. Sc. **124**:375, 1902.

13. Weed, L. H.: J. M. Research **31**:51, 1914.

traced from the subarachnoid space directly through the minute arachnoid villi into the venous sinuses. This was a clear demonstration that the largest part of the absorption must take place in these regions. A very small amount of absorption along the trunks of spinal and cranial nerves was also indicated. There were no granules in the ventricles, in the choroid plexus or in the perivascular spaces. Weed concluded that normally no absorption takes place within the ventricles, and that the fluid in the perivascular spaces usually empties into the subarachnoid space, thus constituting an additional small source of cerebrospinal fluid.

The mechanism of absorption through the thin membrane of the arachnoid villus has generally been accepted as simple filtration or osmosis. The most important researches on this point are those of Dixon and Halliburton,[14] in 1916, who found that the rate of disappearance of foreign substances injected into the subarachnoid space varied inversely with the size of the molecules of the injected substance, and those of Weed and his associates,[7] from 1919 to 1921, who found that the cerebrospinal fluid pressure was always higher than that in the superior sagittal sinus, unless the osmotic pressure of the blood was greatly increased by means of a hypertonic intravenous injection. They also found that the rate of cerebrospinal fluid absorption was conspicuously increased after such hypertonic injections.

It may be accepted as an established fact that the choroid plexus is the chief source of the cerebrospinal fluid, the perivascular spaces contributing a small additional amount, and that the absorption takes place chiefly through the arachnoid villi into the venous sinuses of the skull, a small amount of fluid being absorbed along the cranial and spinal nerve trunks. There is also good evidence that the mechanism of absorption through the arachnoid villi is determined by the relative hydrostatic and osmotic pressures of the cerebrospinal fluid and the blood in the dural sinuses.

SECRETION AND DIALYSATE THEORIES

Two important theories as to the nature of the cerebrospinal fluid have been developed: one, that it is actively secreted by the cells covering the choroid plexus, as suggested by Faivre [3] in 1854 and Luschka [15] in 1855; the other, championed by Mestrezat [16] in 1912, that the fluid is a dialysate in equilibrium with the blood plasma, the choroid plexus acting as a simple dialyzing membrane.

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14. Dixon, W. E., and Halliburton, W. D.: J. Physiol. **50**:198 (Feb.) 1916.

15. Luschka, H., cited by Weed (footnote 7).

16. Mestrezat, W.: Le liquide céphalo-rachidien, Paris, A. Maloine et fils, 1912.

In spite of many investigations, neither theory has gained general acceptance. For instance, both Howell [17] and Starling [18] lean toward the theory of active secretion; neither Weed [7] nor Cushing,[19] in recent articles, take a definite stand in the matter, while Buzzard [20] and Greenfield and Carmichael [21] favor Mestrezat's theory of dialysis. Boyd,[22] in 1920, in his textbook on the cerebrospinal fluid, states that "under normal conditions the process is probably one of filtration, but when the choroid gland is stimulated to activity the process becomes one of active secretion."

It is my purpose in this paper to review the evidence and to present certain additional data and considerations, which, taken together, argue strongly that the choroid plexus forms a semipermeable membrane through which the cerebrospinal fluid is dialyzed or filtered as a result of the hydrostatic pressure in the capillaries of the choroid plexus.

THEORY OF ACTIVE SECRETION

Active secretion by a gland connotes a process involving the release of stored energy, and usually the elaboration of some substance newly formed within the cell. That such true secretion may eventually be brought under the laws of physical chemistry is probable, but the mechanism is more complex than dialysis across a semipermeable membrane, whose cells take little or no active part in the process, simply determining the nature and degree of permeability of the filter.

If the cerebrospinal fluid is a true secretion, one must look for some specific product of secretion. This has never been found. Also one must look for mechanisms to stimulate or inhibit the activity of the choroid plexus. If, on the other hand, the choroid plexus is not a gland, but a dialyzing membrane, one must look for changes in hydrostatic and osmotic pressures in the blood to account for increased or decreased fluid formation. One must look for laws that determine the characteristics of such dialyzed fluid, and in a broad sense these laws may be expected to have a general application wherever such simple dialysis takes place, not only in the human organism but also in the whole field of biology.

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17. Howell, W. H.: Textbook of Physiology, Philadelphia, W. B. Saunders Company, 1924, p. 624.

18. Starling, E. H.: Human Physiology, Philadelphia, Lea and Febiger, 1926, p. 376.

19. Cushing, Harvey: Lancet **2**:851 (Oct. 24) 1925.

20. Buzzard, E. F., and Greenfield, J. G.: Pathology of the Central Nervous System, New York, Paul B. Hoeber, 1922, p. 31.

21. Greenfield, J. G., and Carmichael, E. A.: The Cerebrospinal Fluid in Clinical Diagnosis, New York, the MacMillan Company, 1925, p. 28.

22. Boyd, W.: The Cerebrospinal Fluid, New York, the MacMillan Company, 1920, p. 32.

The direct evidence for active secretion rests on the observation that certain agents when introduced into the general circulation cause a real or apparent increase in the rate of formation of the fluid,[23] which is accompanied by well defined histologic changes in the cells covering the choroid plexus.[24] Among the agents that produce these effects are pilocarpine hydrochloride, muscarine, ether, carbon dioxide, epinephrine hydrochloride, solution of pituitary, extract of brain and extract of choroid plexus.

The morphologic changes produced in the choroid plexus cells under the action of these agents consist of an increase in the size of the cells, which may double in height, and a differentiation into two zones, a granular zone at the attached border and a clear zone at the periphery or free border of the cell. These changes, associated with an increased outflow of fluid, form the basis of the secretion theory and for many years were considered similar to the changes found in the cells of such a gland as the parotid during secretion. It is extraordinary that, until six years ago, no one noticed that these changes, namely, the increased size and the formation of a clear zone at the free border of the choroid plexus cell, are the exact opposite of those that occur during active secretion in typical glands such as the pancreas or parotid; for in them the cells become smaller instead of larger, and have the clear zone at the attached border of the cell instead of at the free border. Becht [25] pointed out this discrepancy in 1920 and insisted that these morphologic changes in the cells of the choroid plexus constitute no evidence for active secretion.

Flather,[26] in 1923, in a careful study of the hemosiderin granules and mitochondria of the choroid plexus, was unable to find any evidence for active secretion; while Weed,[27] in the same year, demonstrated that the intravenous injection of distilled water caused the same changes in the cells of the choroid plexus which form the basis of the secretion theory. Not only do these changes constantly occur after the injection of distilled water, but also they are far more striking than the changes produced by any of the other agents. They are likewise accompanied by a large increase in cerebrospinal fluid pressure, and the intensity of the

23. Dixon and Halliburton (footnote 14). Cappelletti, L.: Arch. ital. de biol. **35**:463, 1900. Pettit, A., and Girard, J.: Arch. d'anat. micr. **5**:213, 1902. Meek, W. J.: J. Comp. Neurol. **17**:286, 1907. Weed, L. H., and Cushing, Harvey: Am. J. Physiol. **36**:77, 1915. Frazier, C. H., and Peet, M. M.: Am. J. Physiol. **35**:268, 1914.

24. Pettit and Girard (footnote 23, third reference). Meek (footnote 23, fourth reference).

25. Becht, F. C.: Am. J. Physiol. **51**:1 (Feb.) 1920.

26. Flather, M. D.: Am. J. Anat. **32**:125 (Sept.) 1923.

27. Weed, L. H.: Am. J. Anat. **32**:253 (Sept.) 1923.

histologic change as well as the degree of cerebrospinal fluid pressure increase is proportional to the amount of distilled water injected. Weed himself states that "the exact significance of the cell changes still remains a matter of speculation" and "the increased height of the epithelial cells of the plexus and the formation of a peripheral clear zone may be interpreted as evidence that an increased amount of fluid has passed through the choroid plexuses," and again that "the changes in the pressure of the cerebrospinal fluid, effected by the intravenous injection of solutions of various concentrations, must in the final analysis find their explanation in the alteration of the osmotic pressure of the circulating blood."

Summing up these observations, one finds that the direct evidence for secretion rests on morphologic cell changes in the choroid plexus. The changes are, however, exactly opposite to those seen in actively secreting glands. The cell changes regularly accompany any increase in the formation of fluid, and may be regarded as evidence of such increased formation. They in no way indicate active secretion and may be as readily interpreted as evidence for dialysis.

THEORY OF DIALYSIS

Now I wish to bring forward the evidence that points more directly to the theory of dialysis. If the fluid is a dialysate, its rate of formation will be dependent on the capillary pressure in the choroid plexus, opposed to which will be the osmotic pressure of all the substances in the plasma to which the membrane is impermeable—these are for the most part proteins. Rapid increases in the total osmotic pressure of the plasma should diminish the rate of fluid formation, while lowering the osmotic pressure of the plasma, as by dilution with distilled water, should increase the rate of dialysis.

When the total osmotic pressure of the plasma and its protein content are relatively constant, which is true under most physiologic conditions, the rate of dialysis should vary directly with variations in capillary pressure in the choroid plexus. The latter can be increased either by a rise in arterial pressure or by a rise in venous pressure. As Ludwig pointed out, changes in venous pressure are much more directly reflected in capillary pressure than are changes in arterial pressure, because the greatest resistance in the vascular system lies in the arterioles. Hence, one may expect the capillary pressure in the choroid plexus to follow closely changes in cerebral venous pressure.

Becht and his associates,[28] in 1920, under conditions not calculated to change the osmotic pressure of the blood greatly, showed that the conditions associated with increased outflow or increased pressure of the

28. Becht, F. C., and Matill, P. M.: Am. J. Physiol. **51**:126 (Feb.) 1920. Becht, F. C., and Gunnar, H.: Am. J. Physiol. **56**:231 (June) 1921.

cerebrospinal fluid were regularly associated also with a rise in either arterial or venous pressure, and that the fluid pressure followed the venous pressure much more closely than it did the arterial. This indicates, as Leonard Hill insisted, that intracranial pressure follows passively general vascular changes. Becht describes several hundred careful experiments and controls, giving the data in full. He interpreted his results as indicating that the increased fluid pressure or outflow was caused by an increased amount of blood in the cranium, without necessarily any increase in the amount of fluid formed. It will be seen, however, that he found increased fluid pressure or outflow always in the presence of just the conditions necessary to raise the capillary pressure in the choroid plexus. If the fluid is a dialysate, one must always expect an increase in rate of dialysis with increase in capillary pressure. Particularly interesting in this regard is the increased amount of fluid formed after lateral sinus thrombosis, when the venous and capillary pressure increase is limited to the cranium. Equally interesting is the internal hydrocephalus, which follows obstruction of the vein of Galen, a condition that raises the capillary pressure primarily in the choroid plexus.

Thus, the only ways in which the amount of fluid formed, or its pressure, could be altered were procedures that varied either the capillary pressure in the choroid plexus or the osmotic pressure of the plasma, as in Weed's experiments already referred to. These are the data that would have to be found before the theory of dialysis could be accepted; they hardly fit a theory of secretion.

Even more strikingly in favor of dialysis are the results obtained by Foley [29] who, using the Prussian blue granule method elaborated by Weed, showed that under the influence of hypertonic salt solution, injected intravenously, the direction of flow through the choroid plexus could be reversed. While neither Weed nor Nanagas was able to reproduce Foley's results, I believe that they have been confirmed at the Harvard Medical School during the last few months.[30]

The cerebrospinal pressure, then, is normally higher than the cerebral venous pressure, and varies directly with the capillary pressure in the choroid plexus, except when the osmotic pressure of the plasma is changed. If this osmotic pressure is diminished the spinal fluid pressure increases, while if the plasma is made hypertonic the fluid pressure will fall—often to figures well below atmospheric pressure, as Weed has shown; the direction of flow through the choroid plexus then appears to be reversed.

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29. Foley, F. E. B.: Alterations in Currents and Absorption of Cerebrospinal Fluid Following Salt Administration, Arch. Surg. **6**:587 (March) 1923.

20. Forbes, H. S., and Fremont-Smith, F.: Intra-Ocular and Intracranial Pressure: An Experimental Study, to be published in a later issue (Arch. Neurol. & Psychiat.).

ANALOGY BETWEEN CEREBROSPINAL FLUID AND AQUEOUS HUMOR OF EYE

This brings us to a most interesting analogy between the cerebrospinal fluid and the aqueous humor of the eye—an analogy touched on by Thomas Henderson [31] in 1910, but particularly emphasized by Wegefarth and Weed [32] in 1914. The ciliary process, which is the point of origin of the aqueous humor, is histologically similar to the choroid plexus of the ventricles, while the pectinate villi projecting into the scleral venous sinuses form the counterpart of the arachnoid villi. The normal intra-ocular tension is about the same as the cerebrospinal fluid pressure, and Wegefarth demonstrated that the pressure of the aqueous humor, like

Comparison of Plasma and Cerebrospinal Fluid

	PLASMA	CEREBROSPINAL FLUID
	Mg. per 100 Cc.	Mg. per 100 Cc.
Protein	6,200-8,200	Ventricle 5-15; Lumbar 15-40
Chlorides (as sodium chloride)	570-620	720-750

SUBSTANCES APPROXIMATELY EQUALLY DISTRIBUTED BETWEEN PLASMA AND CEREBROSPINAL FLUID

Sodium	Carbon dioxide (higher in cerebrospinal fluid)	Urea
Potassium		Glucose ?
		Lactic acid

SUBSTANCES IN HIGHER CONCENTRATION IN PLASMA

Protein	Magnesium
Total reducing substances	Calcium
Total nonprotein nitrogen	Phosphates
Uric acid	Sulphates
Creatinine	Diastase
Creatine	Lipase
Amino acids	

SUBSTANCES PRESENT IN PLASMA BUT EXCLUDED FROM CEREBROSPINAL FLUID

Fibrin	Lipoids
Bile pigments and other pigments	Cholesterol ?
Bile salts ?	Most ferments, immunologic substances (antibodies, complement, lysins), etc.

that of the cerebrospinal fluid, is normally higher than that in the sinuses into which it drains. Increased intra-ocular pressure follows obstruction to the venous outflow from the eye in the same way as increased intracranial pressure follows obstruction to the venous outflow from the cranium. Hypertonic solutions injected intravenously lower both the intra-ocular and the intracranial pressures.[33] Throughout the range of physiologic experiments on the two fluids, the analogy between them is so complete that it is not reasonable to suppose that there is any fundamental difference in their nature. It is perhaps significant that the aqueous humor of the eye is generally considered a filtrate.

31. Henderson, Thomas: Glaucoma, London, Arnold, 1910.
32. Wegefarth, P., and Weed, L. H.: J. M. Research **31**:167, 1914.
33. Duke-Elder, W. S.: Brit. J. Ophth. **10**:1, 1926.

One will not be surprised to learn, then, that in chemical composition the two fluids appear to be identical. Mestrezat,[34] deserves the credit for emphasizing this important fact, in 1911. He also justly insisted that the chemical composition of a fluid cannot be neglected in considering the manner of its formation; for, in the final analysis, if the laws that determine the composition of a fluid are understood, its nature is known.

COMPARISON OF CEREBROSPINAL FLUID AND PLASMA

In the accompanying table, the cerebrospinal fluid is contrasted with the plasma. So far as is known, there is no substance in the cerebrospinal fluid as it comes from the choroid plexus which is not already present in the plasma. Some substances with large molecules are completely excluded from the cerebrospinal fluid; namely, fibrin, lipoids, most ferments and immunologic substances, all pigments and possibly cholesterol and bile salts. Nearly all other known substances in the plasma are present to some extent in the cerebrospinal fluid, while sodium, potassium, urea, carbon dioxide and possibly glucose are approximately equally distributed between the two fluids. The striking contrast lies in the protein, which is almost absent from the cerebrospinal fluid, and the chlorides, which are present in much higher concentration than in the plasma.

MESTREZAT'S EXPERIMENTS

In spite of these marked differences in the concentrations of individual substances, the total osmotic pressure of the plasma and the cerebrospinal fluid is the same if measured by depression of the freezing point.[16] That two fluids in the body with such chemical differences should have the same osmotic pressure appeared to Mestrezat to be of the utmost importance. He conceived the idea that the high chlorides in the fluid compensated for the absence of protein and other colloid substances present in the plasma, and that the two fluids were essentially in osmotic equilibrium.

In order to study this matter he prepared a collodion sack of known permeability so that it would allow the free passage through its walls of all substances present in the plasma except protein. He filled the sack with the cerebrospinal fluid of an ox and immersed it in a large volume of plasma taken from the same animal. Then, after waiting for equilibrium to take place, he examined the cerebrospinal fluid within the sack to see what chemical changes had taken place. To understand fully the significance of this experiment, one must bear in mind that the sack was freely permeable to all substances in the cerebrospinal fluid within the sack and to everything in the plasma outside, with the exception of protein. In spite of constant agitation of the plasma, no change in the composition of the cerebrospinal fluid took place. The experiment was repeated in a different manner. Instead of the sack being filled with cerebrospinal fluid, it was filled

34. Mestrezat, W.: Bull. de la soc. chem. **9**:683, 1911.

with salt solution of a concentration slightly less than that of the surrounding plasma. In every case, after equilibrium had taken place, the chloride content of the fluid within the sack had increased to a figure considerably higher than the chloride content of the plasma. In other words, as the salt solution came into equilibrium with the plasma it approached cerebrospinal fluid in its chloride concentration. As a last experiment, Mestrezat immersed an empty sack in plasma; gradually there filtered into it a clear protein-free fluid, which when examined chemically had essentially the composition of cerebrospinal fluid. The same results were obtained when the sack, instead of being immersed in plasma, was sewed into the peritoneal cavity of the rabbit, cat or dog. In other words, Mestrezat was able to obtain, in such a collodion sack placed in the peritoneal cavity of living animals, a fluid that appeared to be identical chemically with the cerebrospinal fluid of the animal, and had the same osmotic pressure as the plasma of the animal.

These experiments, reported by Mestrezat and Ledebt,[35] are of fundamental importance. They indicate that the cerebrospinal fluid is in osmotic equilibrium with the plasma, and that the character of the equilibrium across the choroid plexus is not fundamentally different from that which may occur in other parts of the body, or across a suitably prepared collodion dialyzing membrane.

It would appear that Mestrezat's experiments were well controlled, crucial and conclusive. Nevertheless, his conclusion that both aqueous humor and cerebrospinal fluid are equilibrated dialysates has not been widely accepted, nor are his experiments referred to by most writers on the subject.

THE AUTHOR'S EXPERIMENTS

Because of these facts, it seemed worth while to attack the problem from a slightly different angle. If the high chlorides in the cerebrospinal fluid depend on the much higher protein content of the plasma, then variations in the protein content of the plasma should cause variations in the distribution of chlorides between the two fluids. For the last eighteen months, Miss M. E. Dailey and I have been studying this matter. We have compared simultaneous samples of human plasma and cerebrospinal fluid in more than 125 instances. The details of these data will be reported elsewhere.[36] Briefly, we have found that a relationship does exist between the concentration of plasma protein and the distribution of chlorides, so that the greater the protein content of the plasma, the greater the excess of chlorides in the cerebrospinal fluid. Kubie and Shults,[37] at Johns Hopkins University, have found the same relationship to hold true for dogs. We have found that this equilibrium is not confined to the cerebrospinal fluid, but is quite analogous to that between plasma and pleural, ascitic or synovial effusions which we have

35. Mestrezat, W., and Ledebt, S.: Compt. rend. soc. de biol. **85**:55 and 81, 1921.

36. Fremont-Smith, F., and Dailey, M. E.: To be published.

37. Kubie, L. S., and Schults, G. M.: J. Exper. Med. **42**:565 (Oct.) 1925.

studied in more than thirty instances. This brings our results in line with those of Loeb, Atchley and Palmer [38] who, in 1921, found that a simple membrane equilibrium exists between plasma and ascitic or pleural effusions, and also in line with the distribution of chlorides between red blood cells and plasma as studied by Van Slyke, Wu and McLean [39] in 1923. It is probable that the Donnan membrane equilibrium plays a significant rôle in determining this distribution of chlorides, although from our data we cannot expect a quantitave demonstration of the theoretical ratio.

Other important work bearing on this aspect, and in accordance with our conclusions, is that of Pincus and Kramer,[40] in 1923, who studied the distribution of anions and cations between plasma and cerebrospinal fluid, that of Bengt Hamilton,[41] in 1925, who studied chlorides, carbon dioxide and total base equilibrium, and that of Lehmann and Meesmann,[42] in 1924, who studied the membrane potential as related to the p_H, chloride and protein distribution between plasma and both aqueous humor and cerebrospinal fluid.

One other relationship should also be true; if the high spinal fluid chlorides are related to the absence of protein, then, when the protein of the spinal fluid becomes very high, approaching that of the plasma (as below spinal cord tumors), one should expect the chloride content of the spinal fluid to be proportionately reduced, approaching the level of the plasma. This we have found to be the case in the few fluids of this nature that we have had the opportunity to examine.

NECESSARY FURTHER INVESTIGATIONS

There are certain aspects of the composition of the fluid that are not clear. An explanation of the low uric acid content of the fluid as compared with the plasma is needed; the same applies to calcium, phosphorus and possibly to magnesium. These relationships are of importance; but they form only a small percentage of the total substances found in the fluid. Further investigations are needed in regard to the exact distribution of carbon dioxide, urea and glucose—the latter forms only a part of the reducing substances which are called "blood sugar."

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38. Loeb, R. F., Atchley, D. W., and Palmer, W. W.: J. General Physiol. **4**:591 (May) 1922.

39. Van Slyke, D. D., Wu, H., and McLean, F. C.: J. Biol. Chem. **56**:765 (July) 1923.

40. Pincus, J. B., and Kramer, B.: J. Biol. Chem. **57**:463 (Sept.) 1923.

41. Hamilton, Bengt: J. Biol. Chem. **65**:101 (Aug.) 1925.

42. Lehmann, G., and Meesmann, A.: Klin. Wchnschr. **3**:1028, 1924; Arch. f. d. ges. Physiol. **205**:210, 1924.

The manner in which further knowledge may clear up some of the doubtful points is well illustrated by the case of potassium. Most investigators have found that the potassium content of the cerebrospinal fluid amounted to only 60 per cent of that of the plasma. This argued against a membrane equilibrium, but recently MacCallum [43] has found that the micromethods used for determining potassium are not accurate. Using large quantities of plasma and cerebrospinal fluid, he has demonstrated that potassium is present in approximately equal amounts in plasma and in cerebrospinal fluid.

Summing up these observations, we find that there is no good evidence for secretion. The variations in pressure of the fluid can be accounted for by the changes that occur in capillary pressure in the choroid plexus or in osmotic pressure of the plasma. The chemical composition of the fluid, as far as all the major constituents are concerned, is exactly what would be expected from a simple membrane equilibrium, and can be reproduced outside the body by simply dialyzing plasma through a suitable collodion membrane. The laws which characterize this equilibrium hold true in many parts of the body and determine the composition of pleural, ascitic and synovial effusions, also the chloride exchange that occurs between red cells and plasma.

CHANGES BETWEEN PLASMA AND RED CELLS DURING CIRCULATION

The rapid advance in our knowledge of the blood and plasma has culminated in the nomogram, described by Henderson and his associates.[44] This is a graphic representation of all the known changes that occur between plasma and red blood cells during the complete cycle of the blood from lungs to tissues and back to lungs again. The knowledge of the fluid exchange between blood and tissues, however, is relatively incomplete. From the arterial side of the capillaries of the tissues, a fluid escapes through the thin endothelial walls and bathes the tissue cells; it then is reabsorbed into the blood stream. The nature of this fluid is little known, since it is not present in sufficient quantity for examination. Yet this is the fluid that nourishes the cells of the body and receives waste products from these cells. It is known, however, that in most parts of the body the capillaries are not permeable to protein,[45] and hence the fluid that escapes from them must be essentially protein-free. Figure 1 shows the relationships for any capillary, and figure 2 shows

43. MacCallum, A. B.: Presented before the Federation of Am. Soc. for Exper. Biol., Cleveland, Ohio, Dec. 28, 1925.

44. Henderson, L. J.; Bock, A. V.; Field, H., Jr., and Stoddard, J. L.: J. Biol. Chem. **59**:379 (March) 1924.

45. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922, p. 206.

the analogy for the cerebrospinal fluid; in both cases the fluid is filtered from the arterial side of the capillaries (which are under a higher capillary pressure) across the tissue space, to be reabsorbed into the venous side where the hydrostatic pressure is lower and the osmotic pressure is higher. Here one should observe the close analogy between the protein-free cerebrospinal fluid (or aqueous humor) and the protein-free fluid escaping from the capillaries to bathe the cells of the tissues.[46] If this analogy is justified, one may expect to learn much of this intercellular

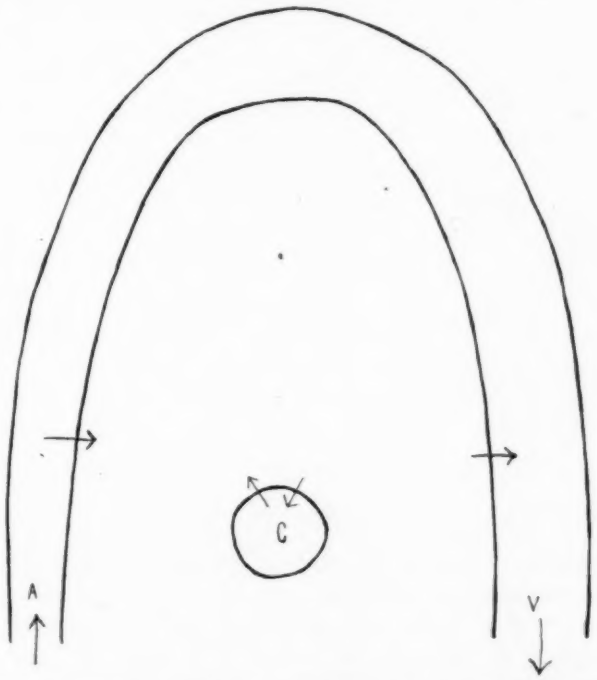

Fig. 1.—Fluid exchange between capillary and intercellular space. Arrows indicate direction of blood flow in the capillary from *A* (arterial limb) to *V* (venous limb) and the direction of fluid filtration across the capillary wall. It is assumed that the capillary pressure is greater than the osmotic pressure of the plasma proteins in the arterial limb and less than this osmotic pressure in the venous limb. The protein-free fluid filtering from the arterial limb is analogous to the cerebrospinal fluid, modified, no doubt, by exchange with tissue cells *C* which nearly fill the tissue space.

46. The suggestion that the cerebrospinal fluid is analogous to the intercellular fluid in other parts of the body was presented before the Federation of American Societies for Experimental Biology, Cleveland, December, 1925, and appears in the Scientific Proceedings of the Am. Soc. for Pharm. and Exper. Therap. (Fremont-Smith, F., and Dailey, M. E.: J. Pharm. Exper. Therap. **27**:255, 1926). Mestrezat independently reached the same conclusion in a paper presented before the Twelfth International Physiological Congress, Stockholm, August, 1926.

fluid by studies of the cerebrospinal fluid, and the latter will have a general significance for the organism which it could never have as a secretion.

There is another protein-free fluid in the body which is just beginning to be investigated in a quantitative way. I refer to the glomerular filtrate of the kidneys, first investigated by Wearn and Richards.[47] This filtrate is characterized by: a protein-free fluid, containing urea in about the same concentration as in the plasma; slightly less sugar than the plasma, but with the chloride content considerably higher than that of the plasma. Although the quantitative analysis of such small amounts

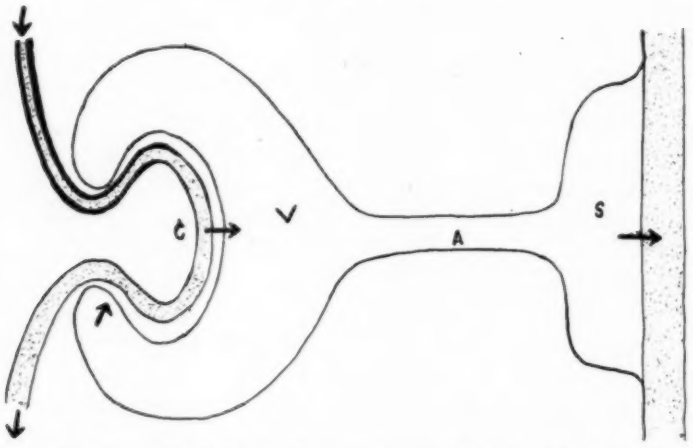

Fig. 2.—Cerebrospinal fluid circulation: the mechanism of hydrocephalus. The direction of blood flow through the choroid plexus *C* is shown by arrows. Heavy lines indicate the thick-walled artery entering the choroid plexus in contrast with the thin-walled vein leaving the choroid plexus.

An arrow indicates the filtration of cerebrospinal fluid from the capillary of the choroid plexus (arterial blood) at *C* into the ventricle *V*. After passing through the aqueduct of Sylvius *A*, the fluid enters the subarachnoid space *S* from which it is reabsorbed into the dural sinus (venous blood) as indicated by an arrow. It should be noted that here, as in figure 1, filtration takes place from arterial blood and reabsorption occurs into venous blood. A close analogy may be found in the formation and absorption of the aqueous humor and also of the glomerular urine.

If reabsorption of cerebrospinal fluid is prevented, for instance, by an obstruction at *A*, the pressure in the ventricle will rise. Filtration through the choroid plexus into the ventricle, however, will not cease, because with every increase in intraventricular pressure there will be a corresponding rise in capillary pressure in the choroid plexus and filtration will continue. This rise in capillary pressure is caused by the fact that the thin-walled veins of the choroid plexus are directly exposed to the intraventricular pressure. When the latter rises the pressure in these veins is also raised, leading to a higher capillary pressure in the choroid plexus and the formation of more cerebrospinal fluid. Thus a vicious circle is established. Similar considerations apply to the mechanism of glaucoma.

47. Wearn, J. T., and Richards, A. N.: Am. J. Physiol. **71**:209 (Dec.) 1924.

of fluid needs confirmation, and the fluid examined was from the frog, nevertheless the relationships of this glomerular filtrate to the plasma is strikingly like that of the cerebrospinal fluid.

If the cerebrospinal fluid is to be considered as a filtrate or dialysate, how, on this basis, may some of the problems of intracranial pressure be explained? I will take one example—hydrocephalus. If the cerebrospinal fluid is a filtrate, when the outflow from the ventricles is obstructed, why does the pressure in the ventricles keep mounting to higher and higher levels and so produce internal hydrocephalus? Figure 2 illustrates this mechanism. As has already been seen, the pressure at which the fluid comes across the choroid plexus will be equal to the capillary pressure minus the osmotic pressure of the plasma proteins, and under most conditions will vary directly with the capillary pressure in the choroid plexus. The actual intraventricular pressure, however, can never be as high as the pressure at which the fluid is formed because of the continuous outflow. In figure 2 one can follow what must happen when this outflow is stopped, or the absorption of fluid prevented by any cause, as for instance by an obstruction to the outflow from the ventricles at *A*. First, the pressure in the ventricles will rise till it equals the pressure at which the fluid is formed. At this point filtration should cease and would do so if it were not for a vicious circle that is immediately set up. When obstruction occurs and the intraventricular pressure rises, this increase of pressure will be felt by all structures within the ventricles, including the thin walled veins of the choroid plexus. The pressure in these veins will be correspondingly raised, and this will at once raise the capillary pressure in the choroid plexus; more fluid will then be formed. Thus, the vicious circle is established. This is equally true as an explanation of the mechanism of the progressively increasing pressure in glaucoma. In both glaucoma and hydrocephalus, the limiting factor will be the highest capillary pressure obtainable. This pressure should be near the arterial diastolic pressure. It is significant, then, that the highest pressure ever recorded either in the eye or in the cerebrospinal fluid is about 80 mm. of mercury.

CONCLUSIONS

In conclusion, I would say that there is no good evidence for the secretion of cerebrospinal fluid; that the evidence taken as a whole is overwhelmingly in favor of dialysis, and that the laws which determine the simple membrane-equilibrium existing between the plasma and the cerebrospinal fluid have a fundamental significance for the mechanism of fluid exchange in the organism.[48]

48. The discussion of this paper has been published in the Society Transactions of the Boston Society of Neurology and Psychiatry (Arch. Neurol. & Psychiat. **16**:245 [Aug.] 1926) and also will be found in the author's reprints.

Clinical and Occasional Notes

INTERNAL HYDROCEPHALUS AND HYPOPITUITARISM*

E. B. Fink, M.D., Chicago

Experimental studies indicate that most of the so-called pituitary syndromes are not due to disturbances in the pituitary body, but are the result of lesions in the centers at the base of the brain.[1] Roussy[2] maintains that the only proved function of the hypophysis is an influence on growth, due to the anterior lobe. Hyperfunction of this portion of the gland leads to acromegaly and gigantism, while hypofunction produces dwarfism. The number of careful pathologic studies of the changes in the hypophysis produced by internal hydrocephalus is extremely small. The clinical picture most commonly produced is dystrophia adiposogenitalis. Anatomically, two types of hydrocephalus are found: primary hydrochephalus, the etiology of which is obscure, and secondary hydrocephalus, usually due to brain tumor.

In 1909, Marinesco and Goldstein[3] reported two cases of dystrophia adiposogenitalis which showed internal hydrocephalus at necropsy. One was secondary to a tumor of the cerebellum, while the other apparently was primary. The changes in the hypophysis were interpreted as passive congestion. One of Cushing's[4] series (case 42) presented a large endothelioma of the right hemisphere causing hydrops and hour-glass distention of the third ventricle. The hypophysis was flattened and contained a colloid cyst of the posterior cleft. A case reported by von Jaksch[5] showed dilatation of the lateral and third ventricles with protrusion of the floor of the third ventricle. The only change in the hypophysis was an adenoma of the anterior lobe, 3.5 mm. in diameter. Bonhoeffer[6] reports a case of idiopathic hydrocephalus with adiposity, in which necropsy disclosed marked protrusion of the infundibulum and marked flattening of the hypophysis. The condition in the patient observed by Cassirer and Lewy[7] was diagnosed clinically as a lesion of the hypophysis but anatomically proved to be hydrocephalus with marked involvement of the infundibular region. The hypophysis was intact. Pollock[8] records a case of adiposity showing sexual infantilism and retarded mental development.

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1. Aschner, Bernhard: Pflüger's Arch. f. d. ges. Physiol. **146**:1, 1912. Camus, J., and Roussy, G.: Presse méd. **22**:517, 1914.

2. Quoted in Paris Letter: J. A. M. A. **86**:964 (March 27) 1926.

3. Marinesco, G. and Goldstein, M.: Nouv. iconog. de la Salpêtrière **22**: 628, 1909.

4. Cushing, Harvey: The Pituitary Body, and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912, p. 208.

5. Von Jaksch, R.: Med. klin. **8**:1931, 1912.

6. Bonhoeffer, K.: Arch. f. Psychiat. u. Neurol. **49**:1, 1912.

7. Cassirer, R., and Lewy, F. H.: Monatschr. f. Psychiat. u. Neurol. **54**: 267, 1923.

8. Pollock, L. J.: Hypopituitarism in Chronic Hydrocephalus, J. A. M. A. **64**:395 (Jan. 30) 1915.

Necropsy revealed internal hydrocephalus and bulging and cystlike distention of the third ventricle, which was the size of a large walnut. Kron[9] reports the case of a woman with evidence of increased intracranial pressure, generalized adiposity and cessation of the menses, in which a diagnosis of tumor of the hypophysis was made. At necropsy were found chronic leptomeningitis with hydrops of a number of ventricles and marked protrusion of the infundibulum.

The first extensive study of the effect of hydrocephalus of the third ventricle on the underlying structures was made by Stumpf.[10] In mild grades of increased intracranial pressure, the anterior wall of the sella turcica becomes flattened, producing an increase in its normal convexity. The bone at this point is so thin that it easily gives way and breaks through to the sphenoidal sinus. The thin lamina terminalis of the anterior wall of the ventricle becomes pushed forward, and there is an increased accumulation of fluid in the recessus optici lying in front of the infundibulum. With increase in pressure, the dorsum sellae becomes flattened anteriorly so that the posterior clinoid processes appear more widely separated. This may cause the hypophysis to lie in the posterior portion of the sellar space and result in flattening of its anterior part, through an increase in transverse diameter. Frequently there is a platelike flattening of the upper surface, in the depth of which the infundibulum enters the glandular portion. In other cases there is deepening of the floor in which the hypophysis lies, flattened and concave on its upper surface. Macroscopically, the posterior lobe is not changed in outline.

When protrusion is marked, the ventricle is a thin, almost transparent bladder, which bulges into the widened sellar floor and produces a marked change in appearance of the entire organ. The anterior portion appears as a broad flat structure, not more than 1 mm. thick. The neural portion is also markedly altered in form. It becomes drawn out into a narrow band, barely recognizable with the naked eye. Except in extraordinary protrusion of the ventricular wall, Stumpf has never seen the infundibulum resemble a cystic dilatation. The anterior lobe is usually affected first. Even with a high grade of increased pressure, the structure of the hypophysis is well preserved.

The only reported case of nanosomia pituitaria secondary to hydrocephalus of the third ventricle that I have been able to find after a careful search of the literature is the one reported by Schultz.[11] A youth, aged 18, developed meningitic symptoms ten years before death, and from that time had severe headaches. After a number of years, a general inhibition of growth was noted, associated with marked underdevelopment of the genitalia and increased deposition of subcutaneous fat. At necropsy, the clinical picture and sudden death were found to be due to high grade hydrocephalus. There was marked dilatation of the third and fourth ventricles. The thin lamina terminalis extended over the chiasm like a bladder. The sella turcia was deeper than normal. The hypophysis occupied only the lower half of the sella, was somewhat flattened from above downward and slightly smaller than normal. The anterior lobe was more compressed than the posterior. The infundibulum was short and plump, and was barely a definite structure. The recessus infundibuli was short and wide, and the region of the tuber cinereum was enormously dilated, its lower border a lamella almost as thin as paper. The markedly compressed opticum chiasma had changed its relation to the infundibulum.

9. Kron. J.: Ztschr. f. d. ges. Neurol. u. Psychiat. **69**:34, 1921.
10. Stumpf: Virchows Arch. f. path. Anat. **209**:339, 1912.
11. Schultz, Arthur: Virchows Arch. f. path. Anat. **248**:180, 1924.

Microscopic study of the base of the brain showed that the infundibulum and the anterior portion of the tuber cinereum were markedly compressed and thinned. In the nucleus paraventricularis, there was evidence of slight destruction of ganglion cells and fibers. Only a number of fibers entering the nucleus showed degenerative changes. Considering the great pressure to which the walls of all the ventricles were subjected, the change in topography of the individual nuclei was almost negligible. The posterior lobe of the hypophysis showed no notable change in structure and composition. The anterior lobe was characterized by a sparsity of typical chief cells. The chromophil elements were far in the majority. Schultz concludes that pressure of a high grade hydrocephalus developing in childhood exerts its deleterious effect particularly on the anterior lobe of the hypophysis. The structural change resulting from this injury is an incomplete maturation of the epithelial cells of the anterior lobe, particularly the basophil elements, causing inhibition of growth (ateliosis) and hypoplasia of the genitals.

REPORT OF CASE

Clinical History.—M. K., a Polish housewife, aged 21, entered the Cook County Hospital, Dec. 16, 1922, complaining of dimness of vision, dizziness and headache of six months' duration. She said that since June, 1922, she had had "neuralgia" of the head. At that time she had been treated in a hospital for a short period. The pain had been relieved temporarily, but she had begun to see double. About November, 1922, she had noted gradual failure of vision until at the time of admission she was unable to see. Headache, the first symptom noted, about June, 1922, usually began at the back of the neck and was associated with dizziness and fainting spells. Sometimes dizziness came on suddenly when the patient was walking along the street. Loss of vision came on gradually and was noticed while sewing. Vision had gradually diminished until at the time of examination she could not distinguish objects. There was no history of polyuria; she usually urinated once during the night.

Menstruation began at 15; it had since been regular, of the twenty-eight day type, lasting four days; the last period occurred Nov. 21, 1922. At the age of 16, the patient had an operation for goiter. In 1919, she had a "fainting attack" with loss of consciousness lasting about twenty minutes, and three such attacks had occurred during the intervening period. The patient was married, but had had no children. It was learned that she was irresponsible, and had been an inmate of a house of prostitution before marriage. Her father, mother, and ten brothers and sisters were living and well.

Examination.—The woman was fairly well nourished and slender; the height was 5 feet (152 cm.); she was practically blind, but not acutely ill. There was no excessive accumulation of subcutaneous fat; the secondary sex characteristics were normal, and the genitalia were developed in proportion to the rest of the body. Examination of the eyes revealed bilateral congenital lenticular cataracts and marked secondary optic atrophy. Vision in the right eye was limited to hand movements at 8 inches; in the left, there was light perception only. Both pupils were dilated and fixed to light and in accommodation. Routine neurologic examination added nothing to the observations recorded.

Spinal puncture showed the fluid to be under slightly increased pressure; the globulin reaction was slightly positive; there were 53 cells per cubic millimeter, all lymphocytes. The blood and spinal fluid Wassermann tests were negative.

Course.—While in the hospital, the patient was nauseated and frequently complained of severe headache. She did not seem to realize that she was seriously ill, and during periods of relief from headache, was always cheerful. She died suddenly, Dec. 23, 1922, about twelve hours after spinal puncture.

Examination.—Necropsy was performed about twelve hours post mortem. The body was 150 cm. long and weighed 100 pounds (45.4 Kg.). The calvarium was easily removed. The cerebral convolutions were flattened and the sulci partially obliterated. There was a small cyst in the region of the hypophysis (1 by 2.5 by 2 cm.). The hypophysis was flattened and the walls of the sella turcica were thinned.

The right ovary measured 5 by 3 by 0.1 cm. The cut surface showed numerous cysts, up to 1 cm. in diameter, filled with an old blood clot. In the left ovary, about which were many adhesions, was a cyst 1 cm. in diameter filled with clear yellow fluid.

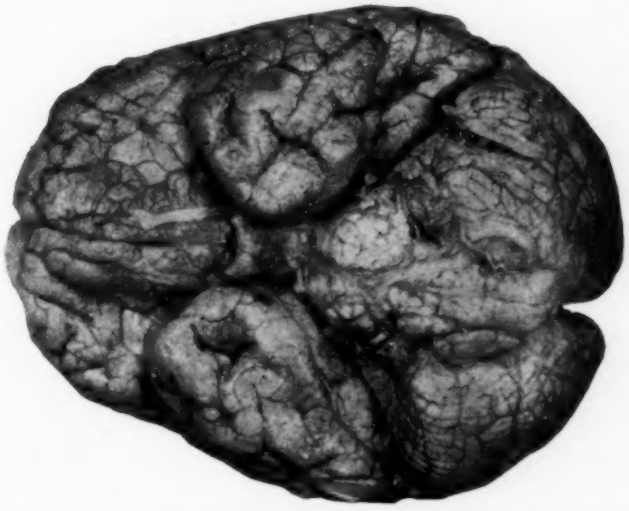

Fig. 1.—Thickened infundibulum showing the bulging of the floor of the third ventricle and compression of the optic chiasm.

The brain, after being hardened in solution of formaldehyde, showed a downward bulging of the floor of the third ventricle, which was 2 cm. in diameter. On longitudinal section of the brain, the lateral, third and fourth ventricles were seen to be dilated and the ependymal lining greatly thickened. The third ventricle measured 2 by 3 cm. The fourth ventricle measured 3 by 4 cm. and had compressed the anterior surface of the cerebellum, the pons and medulla. The lining ependyma was greatly thickened and at the cerebello-medullary angle had closed off the cisterna magna.

The hypophysis was fixed in solution of formaldehyde, embedded in paraffin, and sections were stained with hematoxylin and eosin. In stained sections, the anterior lobe appeared normal in size and shape. Under high power, the vast majority of cells in the anterior lobe were neutrophil chromophobe cells. There was a notable sparsity of eosinophil cells, and the basophils were con-

fined to one area in which there were a number of acini composed entirely of large cells with basophil granules in the cytoplasm. In the posterior lobe, the interstitial tissue was loose and appeared edematous.

The walls of the third ventricle, including the tuber cinereum and hypothalamic region, had undergone complete pressure atrophy.

COMMENT AND SUMMARY

Clinically, this patient presented the picture of brain tumor without localizing symptoms. In general appearance, she resembled the photograph reproduced by Cushing [12] of the Lorain-Levi type of infantilism. The pathologic changes noted were those of internal hydrocephalus with marked protrusion of the floor of the third ventricle, thinning and almost complete atrophy of the tuber cinereum and distention of the infundibulum producing secondary optic atrophy

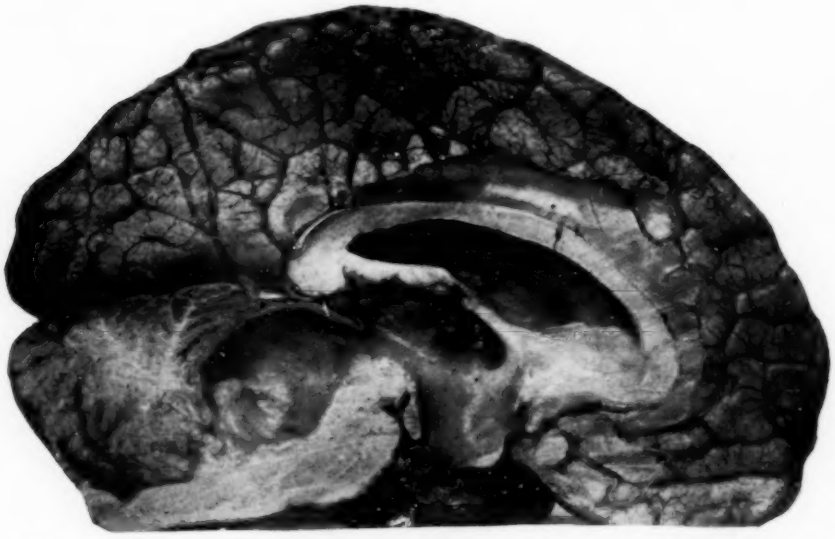

Fig. 2.—Greatly dilated third and fourth ventricles. The floor of the third ventricle is almost as thin as paper, except anteriorly where the compressed optic nerve is shown.

and pressure on the hypophysis. Microscopically, the changes in the hypophysis indicated incomplete ripening of the epithelial cells of the anterior lobe. There was entire absence of symptoms which, from experimental evidence, might be expected to appear as a result of compression of the tuber cinereum and hypothalamic region (polyuria, adiposogenital dystrophy).

Such cases are usually recognized with certainty only at necropsy. Kurt Goldstein [13] mentions as important in diagnosis: the slow onset, a tendency toward remissions which may last from months to a number of years and the absence of localizing symptoms or their fleeting character. The presence of choked disk, the absence of paracentral or cecocentral scotomas and bitemporal hemianopia are points of differentiation from tumors of the hypophysis.

12. Cushing, Harvey (footnote 4, p. 47, fig. 39).

13. Goldstein, Kurt: Meningitis serosa unter dem Bilde hypophysärer Erkrankung, Arch. f. Psychiat. **47**:126, 1910.

SPECIAL ARTICLE

MYASTHENIA GRAVIS*

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During the recent epidemics of so-called lethargic encephalitis, a number of cases presented the syndrome of myasthenia with involvement of the muscles innervated by the motor cranial nerves, which were at times impossible to distinguish from genuine myasthenia gravis. This occurrence has led to renewed interest in the study of the symptom-complex known as myasthenia gravis.

Synonyms for myasthenia gravis are myasthenia gravis pseudo-paralytica; asthenic bulbar paralysis; asthenic paralysis; bulbar paralysis without pathologic lesions; Erb's disease; Erb-Goldflam disease.

HISTORICAL RÉSUMÉ

The disease was first described by Wilkes in 1877, and by Erb in 1878. The latter pointed out that although the clinical picture resembled that of Duchenne's bulbar paralysis, he could not classify it as such. He emphasized the characteristics of the condition as a combination of bulbar symptoms, ptosis and weakness of the muscles of chewing and of the muscles of the back of the neck. After this, practically no observations of note are found in the literature until 1887, when Oppenheim published a report of "a case of chronic progressive bulbar paralysis without anatomic findings." The principal points emphasized in this contribution are the absence of muscular atrophy, the absence of disturbances of electric excitability in the muscles, the frequent occurrence of remissions and the negative anatomic observations. Four years later Goldflam found that in his cases the functional muscular disturbances were not due to an actual paralysis but to an exhaustion of the involved muscles. The nature of this muscle exhaustibility was investigated by Jolly in great detail in 1894, and led to his discovery of the so-called "Jolly" or "myasthenic" reaction. He suggested that the disease be designated as "myasthenia gravis pseudoparalytica," thus removing the general conception, then held, that the disease was confined to the bulb, and focused the attention of observers on the muscles of the body as the site of the disease. In 1900, in contrast to Oppenheim's views, Campbell and Bramwell[1] expressed the belief that muscular atrophies were an

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1. Campbell and Bramwell: Brain **23**:277, 1900.

important component of the clinical picture of the disease. In the same year, Weigert [2] published the report of a case in which he described lymphocytic infiltrations, i. e., lymphocytes in the muscles, which, owing to the fact that the thymus contained neoplastic tissue, he regarded as metastases in the muscles. The next epoch making contribution was that of Buzzard.[3] As a result of a careful clinical and anatomic investigation of five cases this observer concludes that: (1) The disease is one in which the symptoms are not always confined to the motor system, but may include others of sensory, psychic or other origin. (2) In all probability it has a definite and constant morbid anatomy characterized by the presence of widely distributed cellular, and sometimes serous, exudates (lymphorrhages) in the tissues and organs of the body. (3) Slight changes in muscle fiber are frequent, and severe muscular atrophy is a rare occurrence in the disease. (4) Proliferation and degeneration in the thymus are frequent but not constant changes. (5) The symptoms of the disease are best explained by assuming the presence of some toxic, possibly autotoxic, agent which has a special influence on the protoplasmic constituent of voluntary muscle and a less specialized influence on the function of other tissues. (6) The relation of this toxin to the incidence of lymphorrhages and to thymic alterations is not clear.

An entirely new point of view was taken by Markeloff,[4] in 1912, who found that the abnormal fatigue involved not only the voluntary muscles but often also the smooth muscles, the heart, sensory nerves and sense organs, and the psychic life of the individual. This view renewed the discussion of the clinical picture of the disease.

As the number of cases reported in the literature began to increase, and thus far more than 300 cases have been reported, and with advances made in the study of the metabolism and of the glands of internal secretion, numerous attempts have been made to attribute the disease primarily to disordered metabolism and to endocrine dysfunction. These, however, have been too numerous and too fantastic to merit consideration in an historical sketch whose chief aim is to record epoch-making contributions in the history of this most baffling of diseases.

ETIOLOGY

The disease affects females more often than males; it is most frequent between the ages of 20 and 50 years, but it has been observed, though rarely, before 10 and after 50. Mailhouse saw a case in a child,

2. Weigert, Carl: Neurol. Centralbl. **20**:597, 1901.

3. Buzzard, E. F.: Brain **28**:438, 1905; Tr. Path. Soc., London **56**:35, 1905.

4. Markeloff, G. I.: Therap. Obozr., Odessa **3**:585, 1910; Russk. Vrach **10**: 1512, 1911; Obozr. Psikhiat., Neurol. **17**:347, 1912; Arch. f. Psychiat. u. Neurol. **49**:482, 1912.

aged 2½ years; Goldflam [5] in one of 4 years and 9 months, and Kölliker in one of 5 years. One of our patients presented the first symptom of the disease at the age of 69. The persons affected, with few exceptions, are delicate and anemic.

Acute infectious diseases are said to be exciting causes. Von Kétly [6] found twenty-six cases out of 134 following infectious diseases. Remak and Csiky [7] each report a case following influenza; Sinkler's case was preceded by typhoid fever. Grund,[8] Kramer and Gerson each report a case following diphtheria, and Campbell one after scarlet fever. Stiefel's [9] case followed immediately after an attack of acute articular rheumatism. Taylor [10] reports the case of a painter in whom the disease was preceded by lead colic, lead paralysis and lead gout. Hey [11] and Pel [12] each report a case following excessive physical exertion. Another factor of possible etiologic relationship mentioned is pregnancy; Cohn reports a case beginning at the termination of labor, and Goldflam reports one with a recurrence after pregnancy, and another one in which the patient had three pregnancies with a remission of the myasthenia during each one. Tilney [13] reports the case of a woman, aged 24, in whom the symptoms of myasthenia appeared immediately after conception; they increased in severity during pregnancy and were much worse during the puerperium, terminating fatally from respiratory paralysis four weeks after delivery. Burr and McCarthy [14] also report a case that occurred during pregnancy. Hun, Blumer and Streeter [15] collected reports of nine such cases. The striking developmental defects and deformities in the nervous system and in other organs found in many of these patients are believed by some authors to indicate that congenital predisposition plays an etiologic rôle. We will have occasion to refer to this phase of the subject in greater detail in our discussion of the pathogenesis of the disease.

SYMPTOMATOLOGY

The disease is characterized by an incapacity on the part of the voluntary motor system for sustained effort. In an overwhelming

5. Goldflam: Neurol. Centralbl. **21**:97, 1902.

6. Von Kétly, L.: Deutsche Ztschr. f. Nervenh. **31**:241, 1906.

7. Csiky, J.: Deutsche Ztschr. f. Nervenh. **37**:175, 1909; Orvosi hetil. **56**: 1087, 1912.

8. Grund: Deutsche Ztschr. f. Nervenh. **35**:169, 1908.

9. Stiefel, F.: Schweiz. med. Wchnschr. **52**:1056 and 1078, 1922.

10. Taylor, J.: Polyclinic, London **7**:77, 1903; **9**:40, 1905; Proc. Roy. Soc. Med. (Neurol. Sect.) **6**:69, 1912-1913.

11. Hey, J.: München. med. Wchnschr. **50**:1867, 1903.

12. Pel. P. K.: Berl. klin. Wchnschr. **41**:917, 1904; Verhandl. d. Kong. f. inn. Med. **24**:95, 1907; Centralbl. f. alig. Pathol. u. path. Anat. **18**:390, 1907.

13. Tilney, F.: Neurograph **1**:20, 1907.

14. Burr and McCarthy: Am. J. M. Sc. **121**:46, 1901.

15. Hun, Blumer and Streeter: Albany M. Ann. **25**:28, 1904.

majority of cases it begins slowly. It is ushered in with a sensation of general weakness or weakness of some one muscle or group of muscles. It may be preceded by headaches, pains and paresthesias, with a sensation of stiffness in the muscles involved. In the majority of cases the weakness begins in the ocular muscles. Ptosis due to weakness of the levator palpebrae superioris is an early symptom; it may be unilateral. The other extrinsic ocular muscles in the usual order of frequency involved are: the internal, superior and external recti. In Stiefel's case,[9] all external ocular muscles became affected in the course of time. Bielschowsky [16] found in one case weakness of the associated ocular movements and poor convergence. Gowers [17] also described a case showing poor convergence. Hey [11] reports a case in which the external ocular muscles were absolutely free from involvement, whereas Curschmann [18] and Spiller [19] each report one in which the disease was limited only to the external ocular muscles. The former speaks, therefore, of these cases as a "pure ophthalmoplegic form of myasthenia." More recently, Rosenheck [20] has reported a case of myasthenia gravis of five years' duration in which bilateral ophthalmoplegia was the only symptom. Goldflam [5] observed a similar case. As a general rule, it may be said that ptosis is an almost constant symptom, and that this or a diplopia due to external ophthalmoplegia (partial or total) may be the first sign of the disease, and may, in a few cases, be the most prominent symptom.

Next in the order of frequency, the mimic musculature of the face is involved, often, however, not in its entirety, the weakness being confined to individual muscles. Schlesinger reports a case in which the facial muscles were entirely free from involvement. The process then extends to the muscles of speech, next to those of chewing and swallowing and finally to the accessory muscles of respiration and to the muscles of the trunk, arms and legs. Usually, though not always, the muscles which are most constantly called into activity in the daily routine of life show the greatest weakness. The weakness of so many muscles gives the patient a characteristic expression. The double ptosis with the inability to close the eyelids causes a "sleepy" appearance; the facial diplegia renders the face expressionless and apathetic, and the weakness of the orbicularis oris and of the musculi zygomatici gives rise to a peculiar and characteristic laugh, the so-called "nasal smile" or "nasal

16. Bielschowsky, A.: München. med. Wchnschr. **51**:2281, 1904.

17. Gowers, W. R.: Lectures on Diseases of the Nervous System, series 2, lecture IX, 1904, p. 221.

18. Curschmann, Hans: München. med. Wchnschr. **71**:1135, 1924.

19. Spiller, W. G. and Buckman, E. U.: Am. J. M. Sc. **129**:593, 1905; J. Nerv. & Ment. Dis. **32**:469, 1905.

20. Rosenheck, C.: Myasthenia Gravis, J. A. M. A. **72**:1211 (April 26) 1919.

snarl." Because of the weakness of the masseters, buccinators and pterygoids the mouth usually is kept open.

In speaking, the voice, at first normal, soon becomes hoarse, nasal and gradually less and less distinct until complete aphonia sets in. This can best be observed when the patient is ordered to count; as a rule, by the time he has counted up to 40 or 50, he will have become totally aphonic. In many cases, the difficulty of speech may be the first symptom. It may be caused by an inability to move the lips, tongue, muscles of the jaw or the laryngeal muscles, or all of these. While the tongue frequently is involved, all movements of it are not affected to the same extent. In Stiefel's case,[9] limitation of lateral movements after fatigue occurred at the onset of the disease, and later, protrusion of the tongue became impossible, whereas the other movements were intact. Clifford reports a case in which the tongue manifestations occurred only at the onset of the disease, but later the musculature of the tongue functioned normally. Because of involvement of the muscles of chewing and swallowing, eating is a difficult and slow process. This difficulty may consist only of an inability to swallow solid food; in some cases the weakness of the palate and pharyngeal muscles may cause regurgitation of fluids through the nose. In Stiefel's case the palate did not become involved until six years after the onset, when the patient began to regurgitate fluids through the nose and the voice became nasal. Remak observed in his case that during intonation the palatal arch became quickly exhausted. This was also observed by Shaw, Goldflam, Suckling, Mailhouse, Feinberg, Campbell and by us.

Another distressing symptom is dyspnea. It usually occurs in paroxysms that may last from a few minutes to hours. Early in the disease these attacks appear only after exertion, but later are spontaneous. An attack of dyspnea may be sufficiently severe to cause the patient's death. The dyspnea is caused by involvement of the laryngeal muscles and the muscles of respiration. Myasthenia of the laryngeal muscles can readily be demonstrated by the laryngoscope. Thus, Hoppe reports fatigue of the abductors and adductors; Dreschfeld, fatigue of the adductors only; Bernhard of the right vocal cord and Punton of the left vocal cord. Kolischer, Fajersztein,[21] Goldflam[9] and others report involvement of all the laryngeal muscles, with complete aphonia and attacks of dyspnea. The muscles of respiration, the intercostals, the diaphragm and the auxiliary muscles of breathing become readily fatigued after exertion. In some instances strong respiratory movements cannot be performed after physical exertion that involves muscles other than those of breathing. Thus, Levi[22] saw a case in which

21. Fajersztein: Beitr. z. Kenntn. d. Myasthenie, Tübingen, 1902.
22. Levi, E.: Wien. klin. Rundschau **20**:265, 1906.

exertion was always followed by a diminution in the excursions of the diaphragm. Laquer [23] reports a similar case.

Involvement of the muscles of the neck causes the head to fall forward; in some cases the patient actually must support the head with his hands; in others it is held fixed backward in order to overcome the effects of the ptosis and to obtain a wider field of vision. In some instances, the weakness of the muscles of the neck and of the back of the neck may be so profound that the patient is unable to lift the head from the pillow. The weakness of the muscles of the limbs is manifested by the rapid onset of fatigue, usually associated with a rapid pulse and breathing and also by trembling and sweating. The muscles of the trunk show varying degrees of exhaustion; some patients are so weak that they cannot hold up their bodies, so that in attempting to get out of bed they fall to the floor in a heap. The muscles of the trunk and extremities are involved in most cases, though much later than the muscles supplied by the bulbar nerves. Punton reports a case in which the muscles of the extremities remained intact throughout the disease, and Grund [8] reports one in which only these muscles were affected. One of our patients (H. B.) did not show any involvement of the muscles of the trunk, and little of the extremities. There are some cases in which the symptoms referable to bulbar involvement are absent or are only slight, and the brunt of the disease is in the muscles of the limbs, especially in their proximal ends.

Involvement of the special senses is encountered in the form of auditory and visual disturbances. Cases showing a diminution in the range of hearing of high pitched notes, attributed to fatigue of the tensor tympani, have been recorded. Markeloff [4] reports a case in which physical exertion was followed by diminution in the sense of taste and in bone conduction. He attributes the paucity of such reports in the literature to failure to make painstaking detailed examinations in these cases. Lewandowsky,[24] on the other hand, believes that the disturbances of vision and hearing, regarded by those who found them as analogous to the muscular fatigue, are manifestations of hysteria. Lively discussion has arisen concerning involvement of the intrinsic ocular muscles. Kojewnikoff, von Kétly [6] and Mendel report exhaustion of the power of accommodation. Stiefel's [9] patient became rapidly fatigued on attempting to read fine print, but he is not certain whether this exhaustion was one of accommodation or of convergence. Sluggish pupillary reaction to light is mentioned by Rad. Boldt and Markeloff [4] also speak of a myasthenic reaction of the pupils to light. Mendel observed an interesting myasthenic reaction of the pupils to light; at

23. Laquer and Weigert: Neurol. Centralbl. **20**:594, 1901.

24. Lewandowsky: Textbook, Spec. Part **2**:218, 1911.

first the pupil would react promptly, but after a few more attempts were made to elicit the reaction, it would become slow and feeble, but never completely abolished; after a brief period of rest the reaction again would be prompt. Several authors also have reported contracted visual and color fields with disturbances of vision after fatigue. These are attributed to exhaustion of the sphincter iridis. The fundi do not show any changes. As a general rule the muscles of the bladder are not involved. Stiefel's [9] patient suffered from urinary incontinence leading finally to cystitis. Buzzard,[3] Lewandowsky [24] and Rad [25] mention bladder weakness (pollakiuria and vesical tenesmus) which they attribute to involvement of the striated musculus sphincter vesicae externus. Oppenheim [26] does not believe that these symptoms are due to myasthenia.

As to the involvement of smooth muscles, the weight of authority now seems to be against Oppenheim's original dictum that these muscles never are involved. The authors opposed to Oppenheim's view base their conclusions on the numerous cases in which there was indisputable evidence as to the involvement of the intrinsic ocular and bladder muscles. There is abundant pathologic evidence that the cardiac muscle (lymphorrhages) participates in the disease. On the clinical side, Markeloff [4] reports three patients observed by him in whom, after physical exertion, there was an unusual variation in the pulse rate followed by an arrhythmia. Similar cases are reported by Mendel, Senator and Knoblauch.[27] Dupré and Pagniez [28] report a case of sudden death from cardiac collapse in a patient whose heart apparently was unaffected. An electrocardiogram taken in one of our cases (L. G.) shows nothing abnormal, whereas one taken in another case (H. G.) shows only a left ventricular preponderance—an observation of no practical significance.

The cardinal symptom of the disease is the myasthenia. This is neither a paralysis nor a paresis. It is a peculiar tiring of the affected muscles with a gradual loss of power after exertion and rapid recovery after a short period of rest. The muscles involved not only become readily fatigued but also become weak, the weakness persisting even after a complete rest. Curschmann [18] found in his cases that the muscles of the shoulder and pelvic girdles as well as those of the face are more often affected by this persistent weakness or pseudoparalysis (Dauerlähmung), whereas the extrinsic ocular muscles and the muscles

25. Rad: München. med. Wchnschr. **54**:1209, 1907.

26. Oppenheim, H.: Deutsche med. Wchnschr. **30**:1053, 1904; die myasthenische Paralyse, Berlin, S. Karger, 1901.

27. Knoblauch, A.: Frankfurt. Ztschr. f. Path. **2**:57, 1908.

28. Dupré and Pagniez: Nouv. iconog. de la Salpêtrière **18**:247, 1905.

of chewing, swallowing and speech as well as those of the forearms, hands, legs and feet are more often affected by the typical myasthenic fatigue. All observers agree that the myasthenic exhaustion and the permanent weakness of the muscles are two different phenomena. No one has as yet offered a satisfactory explanation for their genesis. An ingenious, though not likely, explanation is offered by Albertoni.[29] He believes that the cause for both the rapid fatigue and the prolonged weakness is to be found in the neural system, and that one neural apparatus exists for intermittent activity, involvement of which produces the rapid fatigue, and another neural apparatus for continuous activity, involvement of which produces prolonged weakness. This combination of fatigue and weakness during a continued voluntary act, such as chewing or speaking, causes the latter to be executed slowly. The tiring and weakness is, in the great majority of cases, limited to the muscles or groups of muscles called into activity during the performance of a voluntary act, but in some cases adjacent or even remote muscles will exhibit the same phenomena. Purely reflex acts, as a rule, do not produce fatigue.

This high degree of exhaustion has been demonstrated repeatedly by means of ergographic curves, which show that contractions obtained during the first movement were of normal strength, but with the continuation of the movement the strength of the contractions diminished rapidly. Thus Stiefel[9] found that in his case the fifteenth contraction after seventy-five seconds of work was one third; the twenty-fifth, after three minutes, one eighth, and the seventieth, after six minutes, one twentieth of the strength of the first contraction. Only a few minutes of rest were necessary for the muscle to regain its original strength. The weakness varies from hour to hour and from day to day. A night's rest or some hours of rest during the day in most cases is sufficient to remove the sensation of fatigue and the actual muscle weakness, the so-called "pseudoparalysis."

Electric Reactions.—Electric stimulation has a similar effect on the muscles. Jolly found that during stimulation of the nerves or muscles by a tetanizing faradic current, repeated at intervals of seconds, the muscular contractions become feebler with each stimulation and finally are abolished completely; but after a short period of rest the muscle regains its normal electric excitability. He also found that the continuous application of the current from a fourth to a whole minute gives rise to a uniform diminution of the contraction, which sooner or later, depending on the strength of the current, disappears completely. Here, too, a rest of barely a minute is sufficient for the muscle to regain its normal excitability. He did not observe these phenomena after galvanism. Laquer[23]

29. Albertoni, P.: Bull. d. sc. med. di Bologna **6**:53, 1906.

and Rautenberg [30] as well as Kollarits,[31] however, claim that they obtained phenomena of muscle exhaustion also after galvanism. According to Buzzard,[3] muscles fatigued by the faradic can still react to the galvanic current. Borgherini [32] found that whereas after faradization a period of recuperation is necessary to obtain a contraction, with galvanism it is only necessary to change the polarity of the current and the muscle immediately will begin to contract again. Exhaustion after cathodal stimulation, according to this observer, does not mean exhaustion after anodal stimulation, and vice versa. All investigators agree that only a short period of rest is necessary for recovery from the exhaustion, no matter by what current the latter is induced. Rautenberg [30] found that contractions of the original intensity can be obtained after a rest period of one-half minute. Curschmann,[18] on the other hand, found that exhaustion following stimulation varied in different muscles in the same subject, but that it took any muscle, whether exhausted volitionally or electrically, the same period of time to recover, namely, two seconds. This view is also shared by Hedinger and others, including ourselves.

Jolly [33] was of the opinion that a muscle exhausted by voluntary movement will not react to faradic stimulation, and that when exhausted by faradism it will not respond to voluntary stimulation. Murri,[34] Massolongo [35] and Keller, on the other hand, found that a muscle which failed to react any more to volitional stimulation would promptly react to faradism, and vice versa. These observations were corroborated by Goldflam,[5] who also established the fact that after exhaustion of a muscle following the stimulation of a definite point (Reizpunkt) the muscle will immediately react when the stimulus is applied at another point. Steinert [36] confirms this observation, as does Murri,[34] who also adduces it in evidence to support his hypothesis that the site of origin of the myasthenic phenomenon is to be sought in the nervous system. We will have occasion to refer again to this phase of the problem when we discuss the pathogenesis of the disease.

The effect of the frequency of the stimulation on myasthenic musculature was investigated by Hoffmann,[37] who found that the greater the

30. Rautenberg: Deutsches Arch. f. klin. Med. **93**:389, 1910.

31. Kollarits: Deutsches Arch. f. klin. Med. **72**:161, 1902.

32. Borgherini: Neurol. Centralbl. **26**:445, 1907.

33. Jolly: Berl. klin. Wchnschr. **32**:1, 1895.

34. Murri, A.: Deutsche med. Wchnschr. **5**:307, 319, 331, 339, 347, 357, 365, 1904.

35. Massolongo, R.: Gaz. hebd. de méd. **97**:1161, 1901; Clin. med. ital. **41**:155, 1902; Riforma med. **18**:197, 1912.

36. Steinert, H.: Deutsches Arch. f. klin. Med. **78**:346, 1903.

37. Hoffmann, A.: München. med. Wchnschr. **51**:1027, 1904.

frequency of the stimulation the more marked was the myasthenic reaction. Exhaustion of a muscle (gastrocnemius) followed stimulation with faradism after seventy-five interruptions of the current a minute, whereas immediate further stimulation with a current that was interrupted only seventeen times a minute still could give rise to strong contractions. This has been confirmed by Harzer.[38]

The effect of the strength of the current on the myasthenic reaction was investigated by Tullio.[39] He found that during indirect faradization the myasthenic reaction could be obtained with a current of any strength, but that this was not so during direct stimulation. In the latter case, feeble currents were followed by normal tetanic contractions; increasing the strength of the current was followed by the appearance of the myasthenic reaction, which disappeared after the use of a strong current, and which was followed by a normal tetanic contraction. Contrary to these observations, Hoffmann [37] could not observe any differences in the effects of strong or feeble currents on the myasthenic reaction. He found that a muscle affected with myasthenia gravis responded to indirect faradic stimulation precisely as does an exhausted curarized muscle to direct stimulation. This led him to conclude that the site of the myasthenic reaction was in the muscle itself.

Steinert [36] investigated the behavior of a previously exhausted muscle when faradic stimulation was persisted in ("Weitreizung"). He found that such muscle, with the persistence of stimulus, ceased to contract for a considerable period, after which it began to contract as strongly as before fatigue had set in; that is, the muscle had recovered its contractility during the refractory period in spite of the protracted stimulation. Kollarits [31] found the same to be true of volitional impulses.

Myasthenic muscle was carefully studied myographically by Rautenberg [31] in one case. He found that after tetanizing stimuli were applied, the contractions finally became somewhat sluggish, the sluggishness increasing with the increasing fatigue of the muscle. This phenomenon he designated "myobradia." During the stage of fatigue, the curves of the contractions were unequal in form and height. Often there would not be a response to a stimulus, so that rhythmically repeated stimuli would give rise to increasingly delayed contractions, which would finally also appear regardless of stimulation—only eight regular contractions following nine stimuli. This phenomenon Rautenberg designated "myautonomy." These "myautonomic" contractions always appeared when the frequency of the stimuli had exceeded a certain number (two or three short tetanizing or four or five strong induction shocks per second). In myasthenic muscle, in contrast to normal

38. Harzer, F. A.: Deutsche Ztschr. f. Nervenh. **47**:207, 1913.

39. Tullio, P.: Ann. di. elett. med. **10**:191, 1911.

muscle, summation of these more frequent stimuli did not occur, but only the rhythmic contractions mentioned above occurred. These rhythmic autonomic contractions did not show evidences of myasthenic exhaustion, but they were extremely sluggish (0.6 seconds in duration). During this "autonomic" condition the muscle was refractory to stimuli other than those maintaining its irritability during the experiment, i. e., it was refractory to additional stimulation. This peculiar phenomenon, according to Rautenberg, is normally observed only in the skeletal muscles of lower animals and in the heart. "Myobradia" and "myo-autonomy," however, are not typical for myasthenia gravis. Rautenberg himself could not demonstrate them in another case which came under his observation, but according to Lewandowsky [24] they are indicative of the individual variations in the muscles encountered in this disease. Sluggish contractions to galvanic stimulation also have been described by Hey.[11]

Investigations as to what effect general exhaustion or fatigue of other muscles of the body had on a given myasthenic muscle led to more or less uniform results. This problem was investigated with a view of determining whether the myasthenia producing agent existed only in the muscle that was myasthenic or whether it was present in the entire body musculature. Mosso and Maggiora established both ergographically and by electric stimulation that a given healthy muscle became fatigued more readily when other muscles had already been exhausted. They also showed that mental fatigue increased muscle fatigue not only to volitional but also to faradic stimulation. Numerous observations showed that myasthenic muscle behaved, in these respects, similarly to healthy normal muscles. Thus Stiefel found in his case that speech disturbances set in much more rapidly when the patient had become exhausted from climbing stairs, and a bad night's rest was always followed by an aggravation of all symptoms. McKendree [40] reports general exhaustion after passive motion of larger groups of muscles. Kuh and Brande [41] report the case of a physician suffering from myasthenia gravis who after passive movements of the upper extremities experienced a sensation of intense general fatigue. Steinert [36] observed a case in which the bulbar symptoms became more severe after extraction of a tooth.

It is important to bear in mind that the myasthenic reaction is variable; it may sometimes be present and at other times absent in the same muscle; it may be present in only a few of the affected muscles; it may be absent at the height of the disease and present during a

40. McKendree, C.: A Case of Myasthenia Gravis, J. A. M. A. **63**:1553 (Oct. 31) 1914.

41. Kuh and Brande: J. Nerv. & Ment. Dis. **40**:617, 1913.

remission, or after all clinical symptoms of myasthenia gravis have disappeared (as in our patients H. B. and H. G.). It may be present in muscles which apparently function normally to volitional impulses. Spiller,[19] for example, reports a case in which clinical evidence pointed to a limitation of the disease to the ocular muscles, but in which the myasthenic reaction could be demonstrated only in one sternocleidomastoid muscle.

The myasthenic reaction is not by any means pathognomonic of myasthenia gravis. It may occur in other conditions, both physiologic and pathologic. We have already cited Mosso, who found a somewhat similar reaction in persons unduly fatigued by excessive intellectual effort. Oppenheim states that he examined fifteen healthy soldiers from this point of view and in not a few of them he found that the contractions, especially in the deltoid, became weaker after from five to six stimulations, which previously would have suggested to him the myasthenic reaction. As far back as 1868, Benedict described an electric reaction of exhaustion occurring in certain paralyses of cerebral origin. Steinert [36] believes that the myasthenic reaction always accompanies cerebral hemiplegia. Kollarits [31] found it in a case of cerebellar neoplasm. Markeloff [4] observed it in a case of familial periodic paralysis, and he therefore speaks of a possible relationship between this disease and myasthenia gravis. Krämer found it in postdiphtheritic paralysis, and Salmon in hysteria, angioneurotic edema, traumatic neurosis and exophthalmic goiter. Köstner found it in a case of carbon disulphide poisoning, and Meyer-Gottlieb in veratrine poisoning. Böhm [42] (Leipzig) and Watts could produce a similar reaction in muscles poisoned by protoveratrine. The literature also contains reports in which the myasthenic reaction was found in cases of Friedreich's disease, chronic poliomyelitis, progressive muscular dystrophy, scleroderma, myotonia and polyneuritis. As one analyzes these cases critically, however, he is impressed with the fact that either the reactions obtained were not true myasthenic reactions, or that the conditions mentioned above were complications of myasthenia gravis and that the reactions obtained were due to the latter. In spite of all these exceptions, the myasthenic reaction is the characteristic symptom of myasthenia gravis. In this connection it must be emphasized that by the weight of authority the muscles in this disease do not show electric changes other than the myasthenic reaction, i. e., there is not a reaction of degeneration.

Muscle Atrophy.—The question as to whether muscular atrophy is a symptom of myasthenia gravis always has been debatable. Oppenheim, as we stated in the historical sketch, insisted that muscular atrophy did not belong to the clinical picture of the disease. Markeloff [4] found atrophy in

42. Böhm, R.: Therap. d. Gegenw. **45**:489, 1904.

two of his seven cases, and he collected from the literature reports of 200, twenty-eight of which showed definite muscular atrophy. To this number, reports of three cases published by Levi may be added. Markeloff attached significance to the fact that the amyotrophy usually involves the same group of muscles that is affected by the myasthenia. Stiefel's case showed neither atrophy nor reaction of degeneration, but twelve years after the onset, though the muscles in general still showed good nutrition, he noticed fibrillary twitchings of the tongue. Remak and Liefmann's [43] case showed fibrillary twitchings and hemiatrophy of the tongue. Pel [12] saw a case with typical myasthenia, lingual atrophy and reaction of degeneration. Similar cases are reported by Buzzard [3] and also by Kojewnikoff. Laquer [23] believes that the muscle fatigue is a precursor to the atrophy. Curschmann [18] has called attention to the fact that when muscular atrophy does occur, it usually is limited to the muscles ordinarily involved in Erb's type of muscular dystrophy. Stcherbak [44] reports a case of myasthenia gravis in which one group of muscles showed diminished electric excitability and another group was hypertrophied. Fajersztein [21] is of the opinion that amyotrophy belongs to the clinical picture of the disease. Our cases did not show any wasting; nevertheless we believe that cases of long duration do show amyotrophy, but that it is generalized, nondegenerative in nature and most probably caused by disuse.

Muscle Tonus.—This, as a rule, is normal; severe cases show hypotonia of the affected muscles during the stage of exhaustion. Dupré and Pagniez [28] report a case showing severe hypotonia, and in one of Steinert's [36] cases the hypotonia was so marked that tendon reflexes could not be elicited. Oppenheim, however, who saw Steinert's patient, had some doubts as to whether it was a case of uncomplicated myasthenia. Herzog reports a case showing rigidity of the muscles of the lip and of the small muscles of the hand; as a result of the latter the patient had great difficulty in extending the fourth and fifth fingers (phenomena not unlike those observed in tetany); examination showed increased tonus in the muscles mentioned above, but because of the absence of the Trousseau, Chvostek and Erb phenomena Herzog does not attribute the hypertonicity to tetany.

Reflexes.—The pupillary reflexes have been discussed under the heading of muscular involvement. Early in the disease the palatal reflex is normal, but it may become diminished with the onset of symptoms referable to the palate; this is attributed to myasthenia of the palatal muscles and not to disturbances in the innervation of the palate. Absence of the pharyngeal reflex has been observed by Oppenheim.

43. Liefmann: Deutsche Ztschr. f. Nervenh. **21**:159, 1902.
44. Stcherbak, A.: Rev. neurol. **17**:539, 1909.

The tendon reflexes generally are normal; occasionally they are diminished; often from twenty to forty percussion taps of the tendons are followed by a progressive diminution of the reflexes, and finally, by abolition with a return to normal after a few minutes rest. Exhaustibility of the knee reflexes is reported by Kolischer, Collins, Osann,[45] Burr,[46] Strümpell,[47] Markeloff,[4] Patrick,[48] Knoblauch,[27] Curschmann [18] and others. Hahneman reports a case showing absent Achilles reflexes. Transitory ankle clonus was observed by Shaw and Goldflam. This is not significant because as Tileston and, recently, J. S. Galant [49] have shown, transitory ankle clonus may appear in all conditions of exhaustion without the presence of anatomic changes in the nervous system. The superficial reflexes are unaffected, although there may be difficulty in eliciting them in cases in which the corresponding muscles are myasthenic.

Sensation.—As a rule sensory disturbances are not present. Generalized pains, headaches and a feeling of stiffness, especially in the facial muscles, may occur. Hey,[11] Buzzard,[3] Sossedorf and others report cases showing rheumatoid pains. Senator observed a case with a zone of anesthesia over the chin. Buzzard saw one case which began with pain in the lower extremities and objective sensory disturbances in the ulnar distribution of both arms and hands; another one of his cases began with pains in the shoulders, arms and legs and a sensation of pins and needles in the tips of the fingers; the pains were sharp and intermittent and grew worse in rainy weather; objectively, there were small areas of relative analgesia and anesthesia, but because of the patient's mental condition these were not definite; another patient complained of vague pains and stiffness of the lids on awaking in the morning; another developed, seven years after the onset, a dull aching pain in the right arm and leg especially after exertion. In view of these observations Buzzard states that, although Campbell and Bramwell [1] (1900) claimed that there were not any sensory disturbances in this disease, their presence cannot longer be held to be sufficient to throw doubt on the diagnosis of myasthenia gravis. Markeloff,[4] Albertoni [29] and Salmon [50] report diminution of cutaneous sensibility to electrocutaneous stimulation. One of our patients complained of headaches, two of pains in the back of the neck, and one of pains radiating into the arms; but none showed objective sensory disturbances. In spite of the reported

45. Osann, E.: Monatschr. f. Psychiat. u. Neurol. **19**:526, 1906.
46. Burr, C. W.: J. Nerv. & Ment. Dis. **32**:172, 1905.
47. Strümpell, von: München. med. Wchnschr. **59**:1018, 1912.
48. Patrick, H. T.: Myasthenia Gravis, J. A. M. A. **38**:58 (Jan. 4) 1902.
49. Galant, J. S.: Jahrb. f. Psychiat. u. Neurol. **43**:244, 1924.
50. Salmon, A.: Policlinico **14**:157, 1913.

cases with subjective and objective sensory disturbances, these have, in our opinion, not been sufficiently constant to justify their being included in the symptomatology of the disease.

Vasomotor and Trophic Disturbances.—Raymond and Lejonne [51] found diminution of the blood pressure in one case. Bing also noticed this in one of Oppenheim's cases, as did Patrzek [52] in his case. Diller [53] reports a case with vasomotor disturbances. Cassirer and Oppenheim saw a patient in whom the attacks of myasthenia in the ocular muscles always were accompanied by chemosis, conjunctivitis and exophthalmos. In Stiefel's case, after a definite remission lasting three months, the patient developed an angina that was followed by an aggravation of all symptoms of myasthenia; during this episode transitory swellings of the tongue occurred, which the author believes might have been the result of lymphorrhages in the tongue. The transitoriness of these swellings would suggest to us rather the possibility of a manifestation of angioneurotic edema of the tongue, although Mandlebaum and Celler's [54] patient showed impairment of the movements of the tongue during life, and at necropsy lymphorrhages were found in that organ. Bookman and Epstein's [55] case showed bronzing of the skin and pigmentation of the buccal mucous membrane. Patrzek's [52] case also showed pigmentation of the face but not of the buccal mucous membrane. One of our patients (L. G.), still under observation, has a "greasy" face and pigmentation of the skin of the face, neck and proximal parts of the arms but no pigmentation of the mucous membranes.

Psychic Disturbances.—According to Oppenheim, psychic symptoms do not occur in myasthenia gravis. Buzzard,[3] however, saw one patient with melancholia, delusions of persecution and suicidal tendencies. Markeloff [4] reports one case showing dementia praecox and one apathy, and he believes that mental symptoms do occur in myasthenia gravis. Albertoni and Jung both found retarded association reactions. One of our patients (S. S.) was markedly depressed and had suicidal tendencies throughout the entire period of the disease—two years; after his recovery the depression disappeared, and his mental state has remained normal for eight years. We doubt whether these cases can be regarded as sufficient evidence to include psychic symptoms in the symptomatology of the disease. We believe that they are merely the normal mental reactions for a person affected with a chronic disease of such disabling character.

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51. Raymond and Lejonne: Rev. neurol. **14**:709, 1906.
52. Patrzek: Ztschrft. f. d. ges. Neurol. **63**:155, 1921.
53. Diller, T.: J. Nerv. & Ment. Dis. **31**:210, 1903.
54. Mandlebaum and Celler: J. Exper. Med. **10**:308, 1908.
55. Bookman, A., and Epstein, A. A.: Am. J. M. Sc. **151**:267, 1916.

Laboratory Observations.—The blood picture in uncomplicated cases is normal. The literature contains reports of cases complicated with Banti's disease and with polycythemia with the usual blood pictures of these conditions. Our patient H. G. showed this condition. Stiefel's case showed, early in the disease, a relative lymphocytosis of 48 per cent (total white cells, 8,400; polymorphonuclear cells, 49 per cent; lymphocytes, 48 per cent; eosinophils, 1 per cent; transitional cells, 2 per cent). Pel's case [12] showed a leukocytosis of 16,000 on the bad days, which would drop to 6,000 on the good days. A similar case was observed by Cohn. Sitsen [56] found leukocytosis with a preponderance of polymorphonuclear cells. Raymond and Lejonne [51] report an increase of lymphocytes in the blood, but they are unable to state whether this lymphocytosis was the result of a chemotaxis induced by a poison circulating in the blood or of a general disturbance in the circulation of the lymph. One of our patients (S. S.) had a white cell count of 11,000 with 46 per cent lymphocytes; the blood of L. G. never showed more than 7,000 white cells, and a normal differential count. On admission, the blood of H. B. showed 105 per cent hemoglobin, 5,664,000 red cells and 13,400 white cells, with 34 per cent lymphocytes. Skinner's [57] case showed a leukopenia. Although Stiefel believes that the variations noted in the blood picture during the bad and the good days is of some clinical significance, we doubt whether there is sufficient evidence to establish any relationship between the occasionally abnormal blood picture and the symptoms of myasthenia gravis.

Metabolic Studies.—The results of metabolic research in myasthenia gravis have been so varied that it is difficult to reach any definite conclusion as to their significance. Boldt [58] and Mohr [59] report large quantities of lactic acid in the urine and blood on the days of work. Kaufmann [60] reports the existence of paralactic acid in the blood and, to a slight extent, in the urine. On the other hand, Spriggs,[61] Bookman and Epstein,[55] and Diller and Rosenbloom [62] could not detect any increase of lactic acid in their cases. Markeloff,[4] as well as Halpern,[63] found an excess of calcium, and speaks of the relationship of this phenomenon to the parathyroids and to myasthenia gravis. Bookman and

56. Sitsen, A. E.: Nederl. Tijdschr. v. Genesk. **1**:1917, 1906.

57. Skinner, E. F.: J. Neurol. & Psychopath. **4**:344, 1924.

58. Boldt, K.: Monatschr. f. Psychiat. **19**:39, 1906.

59. Mohr: Berl. klin. Wchnschr. **46**:1052, 1903.

60. Kaufmann, M.: Monatschr. f. Psychiat. u. Neurol. **20**:299, 1906; München. med. Wchnschr. **54**:756, 1907; Jahrb. f. Psychiat. u. Neurol. **14**:173, 1909.

61. Spriggs: Quart. J. Med. **1**:68, 1907.

62. Diller and Rosenbloom: Am. J. M. Sc. **148**:65, 1914.

63. Halpern: Miecz. Medycyna **47**:914, 1912.

Epstein's figures for calcium were normal; Pemberton's [64] case showed a marked loss of calcium, as did the patient examined by Diller and Rosenbloom. In Chadman and Spiller's [65] case there was a slight calcium retention. In Bookman and Epstein's case the excretion of creatinine was diminished. Diller and Rosenbloom's case also showed a diminished excretion of creatinine, but it was accompanied by a negative nitrogen balance. Spriggs [61] found the creatinine excretion decidedly below normal in his patient. Pemberton's case also showed a diminished creatinine excretion with a normal nitrogen balance. Kaufmann investigated principally the nitrogen metabolism and the ammonia excretion; he found that exercise caused a decrease in the retention of nitrogen and, if continued, a loss together with increased excretion of ammonia; it must, however, be emphasized that in his case the liver was diseased. Williams and Dyke [66] found a marked creatinuria in four cases of myasthenia gravis. One case showed considerable amounts of creatinine in the urine when the patient was on a creatine-creatinine-free diet; two patients were unable to deal with small amounts of creatine when given by mouth; in two cases the percentage of muscle creatine was estimated from biopsy specimens and was found low; in all four cases the glucose tolerance was lower than normal. These authors, therefore, conclude that the diseased muscles are responsible for the altered carbohydrate tolerance and that the creatinuria observed was probably secondary to this defective glucose metabolism. Rolly and Opperman found marked hyperglycemia in one case. Patrzek's [52] case showed hypoglycemia with an unusually low blood pressure, both of which were not influenced by the injection of epinephrine hydrochloride. Spiller and Chadman's patient (examined by Jonas) did not show any creatinuria, which Jonas attributes to the normal or rather increased tolerance for glucose. In Stiefel's case, Loeffler found normal figures for nitrogen and carbonic acid.

In discussing the creatine and creatinine changes, it is important to bear in mind that these substances are related to muscle metabolism, and it has been suggested that in a given case the urinary output of these substances is in proportion to the patient's muscle volume. The creatine coefficient is the number of milligrams of creatinine nitrogen per kilogram of body weight; this is about 8 in men and less in women. Creatinine (the anhydride of creatine) is a normal urinary constituent and remains constant as long as the patient remains on a creatinine-free and creatine-free diet. Creatine is normally found in the urine till

64. Pemberton: Am. J. M. Sc. **139**:816, 1910.

65. Chadman, M. G., and Spiller, W. G.: A Case of Myasthenia Gravis of Slow Development, Arch. Neurol. & Psychiat. **9**:116 (Jan.) 1923.

66. Williams and Dyke: Quart. J. Med. **15**:269, 1922.

the beginning of the second decade of life. Its appearance in the urine after this age is usually pathologic. It may then appear: (1) in cases of low carbohydrate tolerance or insufficient carbohydrate intake, as in starvation from diabetes; (2) in cases with hyperactive metabolism (fever, hyperthyroidism); (3) in cases with muscle wasting (dystrophies). Creatine also appears during pregnancy and the puerperium, and sometimes during menstruation. We emphasize these points because almost all investigators agree that in myasthenia gravis there is a low creatine-creatinine excretion. This fact is interpreted by many as indicating that the disease is one of disordered muscular metabolism. This interpretation finds great support in the fact that in myasthenia gravis the amount of neutral sulphur excreted in relation to the total sulphur is below normal, and Folin claims that the neutral sulphur of the urine represents a partial expression of the endogenous or cellular metabolism in the same manner as does the creatinine and the uric acid excretion.

The phosphorus and fat metabolism are reported by all observers as normal.

It is of interest to note that in all our cases the blood and urinary chemistry did not show any deviation from the normal. The basal metabolic rate in patient H. B. was + 17 per cent seven weeks after admission, and when taken again twelve days later on a restricted diet it was — 11 per cent, with no perceptible difference in the myasthenia as far as one could judge clinically. The basal metabolic rate in L. G. was — 6 per cent, taken on two occasions six weeks apart, with no change in the clinical picture of the disease. It was normal in patient H. G.

Such conflicting reports would, in our opinion, tend to indicate that whatever metabolic changes may occur in myasthenia gravis must be caused by factors other than the disease itself. Indeed, Curschmann [18] goes further than this when he states that "no metabolic changes are found in uncomplicated cases of myasthenia gravis. Changes in the respiratory, calcium, phosphorus and carbohydrate metabolism are to be attributed to the diseases occasionally associated with myasthenia gravis, such as exophthalmic goiter, tetany and diabetes."

Roentgenography.—Roentgen-ray studies, except in cases associated with pathologic change in the thymus, do not show any unusual features.

Spinal Fluid.—In the cases in which examinations of the spinal fluid are reported, as well as in our cases, the fluid was always found normal.

Temperature.—Goldflam [5] observed a rise in temperature in several cases, and Oppenheim found this in one case. The significance of this is not known.

Biopsy Observations.—One of the most important signs in the symptomatology of the disease is the finding of lymphorrhages in muscles excised intra vitam. As a laboratory aid in the diagnosis of myasthenia gravis, it is second to none. However, in order to avoid repetition, we shall reserve the description of their nature and incidence of occurrence for our discussion of the pathology and pathogenesis of the disease.

PATHOLOGY AND PATHOGENESIS

Definite and characteristic lesions have not been found in all cases after death. In more than 50 per cent of the cases, throughout the skeletal muscles and in the other organs, small foci of cells, which have been designated by Buzzard [3] as "lymphorrhages," are found. He chose this designation because: (1) the cells are indistinguishable from lymphocytes by their size, and by the fact that the nucleus generally is round or slightly oval and surrounded by an extremely narrow belt of protoplasm; (2) they infiltrate the tissues in the same way that red blood cells do in cases of capillary hemorrhage, and are not associated with obvious changes in the surrounding structures, inflammatory or otherwise. These collections of cells were first described by Sossedorf, who considered them evidence of an inflammatory or degenerative process within the muscle.

In 1901, Weigert [2] had an opportunity to make a postmortem examination in a case that had presented clinical symptoms of myasthenia gravis. He found numerous foci of small lymphoid cells, throughout which were scattered a few "epithelioid" cells in the deltoid, diaphragm, myocardium and pericardium. The cells were seen diffusely scattered over the external and internal perimysium and in many areas between the muscle fibers themselves which apparently were free from involvement. Having also found a malignant thymic tumor of similar anatomic structure, Weigert was inclined to regard these collections of cells in the muscles as metastases of the thymic tumor. However, as shown by subsequent investigations, the fact that these lymphorrhages could be found in muscles of patients without anatomic evidences of mediastinal tumor or of a persistent thymus cast great doubt as to the correctness of Weigert's interpretation. Others believe them to be an expression of a chronic inflammation, especially when, in addition to the round cells, they also contain polymorphonuclear and plasma cells. Hun, Blumer and Streeter [15] suggest that the myasthenia might be due to some disturbance in the circulation of the blood and lymph in the muscles, and they believe that the lymphorrhages interfere with the free flow of lymph. These authors raise the question whether the lymphorrhages are primary and caused by irritation of some toxin or other cause, or whether they are secondary to a primary change in the lymph circula-

tion; they are inclined to the latter view. Link [67] is also of the opinion that the lymphorrhages prevent the neutralization of the hypothetical fatigue products by interference with the circulation of lymph. He bases his opinion on human experiments in which he was able to check the outflow of blood and lymph in muscles, after which the latter showed rapid fatigue to volitional and faradic stimuli.

In skeletal muscles the lymphorrhages are found not only in the muscle fibers themselves, but also in the fibrous sheath; they are seen better in transverse than in longitudinal section. They have been described as occurring in the ocular muscles, the tongue, heart, liver, suprarenals, thyroid, thymus and pancreas. Their number in any given muscle does not seem to correspond to the degree of weakness of that muscle. Their occurrence is apparently transitory, since they are not more numerous, if as numerous, in long standing cases than in those with an acute and rapidly fatal course. Lymphorrhages also have been found by Buzzard between the cells in the ganglia in some of the thoracic and lumbar nerve roots, and by Mandlebaum and Celler [54] in the perivascular lymph spaces of several small capillaries in the gray matter near the vagus nucleus and in the outer part of the pyramidal tract ventral to the olivary body. In this connection we wish to point out that the inability to find lymphorrhages in a given case does not necessarily mean that lymphorrhages are not present, because it is obviously impossible to examine histologically every muscle and every organ in the body.

There have also been reported changes in the muscles in the nature of protoplasmic degeneration such as fatty degeneration, vacuolization, granulation, plasmoid degeneration and an increase in the interstitial connective tissue (perimysium). Thus, at biopsy, Marburg [68] found by the Marchi method that the muscle fibers were infiltrated with fat droplets in two cases, the infiltrates consisting chiefly of lymphocytes, and of a few leukocytes and plasma cells which he regards as embryonal sarcolemma cells. To him these observations indicate that the disease is a degenerative myositis, toxic in origin. Borgherini [32] reports similar changes and speaks of plasmoid and hyaloid degeneration of the muscles. Other authors report muscular atrophy with a narrowing of the individual fibers and an increase in their nuclei. There is a tendency to an increase in the muscle striations, although in Weigert's case there was a diminution in the transverse striations. Here and there one finds evidence of longitudinal striations. Buzzard,[3] Csiky,[7] Knoblauch [27] and others call attention to the great variability in the staining of the sarcoplasm.

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67. Link, R.: Deutsche Ztschr. f. Nervenh. **23**:114, 1902-1903.

68. Marburg: Ztschr. f. Nervenh. **28**:111, 1907.

In the five cases examined histologically by Buzzard, the muscles showed, in addition to the lymphorrhages, changes usually associated with an early muscular atrophy of toxic origin, and which he says "would have resulted in grave muscular degeneration, had the morbid process at work been further encouraged. They certainly make the occasional occurrence of true muscular atrophy in this disease by no means surprising." The changes were most marked in the fibers adjacent to the lymphorrhages.

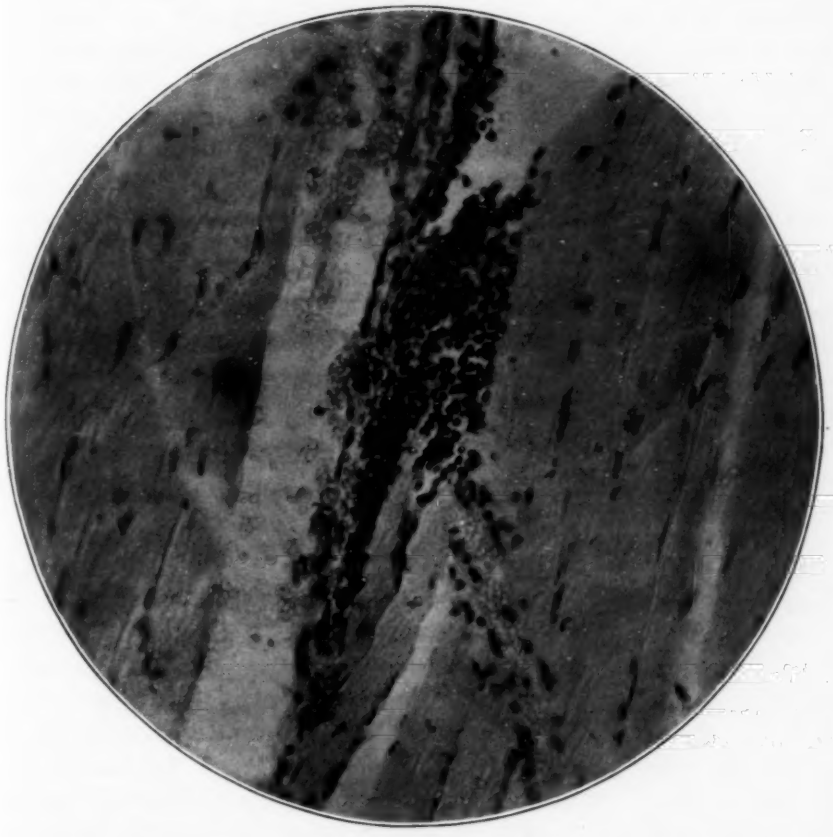

Fig. 1 (H. B.)—Typical lymphorrhage from the left deltoid muscle.

Knoblauch especially points out the frequent occurrence of muscle fibers whose nuclei are deposited in the inner part of the fibers and away from their margins. From his study of the muscles he concludes that two kinds of muscle fibers exist in myasthenia gravis: (1) pale, rapidly exhausting fibers, and (2) red, "fatigue-withstanding" fibers, with a preponderance of the former over the latter; the myasthenic reaction, according to him, is the normal reaction of the pale muscle fibers.

The muscles in Stiefel's [9] case (examined histologically by Heusser [69]) showed changes usually described as simple muscular atrophy; the lesions involved individual fibers or fiber bundles, but not entire muscles. There was not any evidence of degenerative, infiltrating or inflammatory lesions.

In Mandelbaum and Celler's [54] case, the muscles examined showed many lymphorrhages but no inflammatory, degenerative or atrophic changes of the muscle fibers.

Patrzek [52] reports an atypical case of myasthenia gravis, with scleroderma of the face, hands and feet that preceded the myasthenia by two years; biopsy showed interstitial lymphorrhages and pale muscle fibers like those described by Knoblauch. At a necropsy performed by Mathias,[70] degenerative lesions were found in various muscles (pale and grayish white fibers); these lesions were most pronounced in the muscles of the larynx, pharynx, esophagus, diaphragm, pectorals, intercostals and serrati antici. The muscles of the extremities were much better preserved. Vestiges of a thymus could not be found. Mathias designates the condition as "myopathia alba lymphatica asthenica" and believes that it should be included among the heredodegenerative system diseases of the muscles. In Skinner's [56] case a piece of muscle from the calf examined postmortem did not show any typical lymphorrhages, but a marked increase in the sarcolemmal nuclei presented a histologic picture closely resembling that of myotonia atrophica.

It is seen, then, that numerous cases showed pathologically some form of muscle change in the nature of either a simple or a degenerative atrophy or of a myositis. The different observers give different interpretations to these muscle changes, but none of the changes described were found with a sufficient constancy to entitle them to be regarded as an essential factor in the pathologic condition and pathogenesis of myasthenia gravis. The only constant lesion found in the muscles is the lymphorrhages, and these are therefore, by a preponderance of evidence, to be regarded as the one definite and pathognomonic characteristic in the pathologic changes of the muscles in the disease. As far as we could find in the literature, lymphorrhages have never been found in any other disease, except in one case of amyotrophic lateral sclerosis reported by Buzzard. Any attempt to link up these lymphorrhages with the functional disturbance in the muscles, the myasthenia, thus far has been unsuccessful. The fact that muscles show lymphorrhages both at biopsy and necropsy in cases in which intra vitam the same muscles did not show myasthenia ergographically or electrically, and the fact that the degree of functional disturbance in a given muscle

69. Heusser, H.: Schweiz. med. Wchnschr. **52**:1080, 1922.

70. Mathias: Ztschr. f. d. ges. Neurol. **63**:171, 1921.

depends on neither the size nor the number of these infiltrations, as well as the fact that muscles which intra vitam showed myasthenia but no lymphorrhages at any time would seem to be sufficient evidence that, though they are found in a large number of cases, they nevertheless cannot be regarded as a pathogenic factor in the disease. We should be inclined to regard them as a manifestation of the disease rather than its cause. With this in mind, one might regard the other changes reported in the muscles as the result of the same factor or factors that produce the lymphorrhages. In this connection, we also wish to point out that the opinion of those who believe that the disease is heredodegenerative in nature lacks support, if one takes into consideration the clinical fact that in many of the cases which showed muscular atrophy the atrophied muscles were not necessarily the muscles that were mysthenic. That there is not any relation between the atrophy and the lymphorrhages also is obvious from the fact that, in many of the cases reported, the muscle fibers adjacent to the lymphorrhages were normal.

Slight pathologic changes in the nervous system have been reported by various observers. Thus, Mayer found chromatolysis in the cells of the anterior nerve roots in Marchi preparations. Similar changes, either by the Marchi or by the Niss' method, were observed by Kolischer, Guthrie,[71] Leclerc and Sarvonat,[72] Sossedorf, Marinesco and Widal,[73] Fajersztein,[21] Dejerine-Thomas, Liefman [43] and others in the nerve cells or in the intramedullary root fibers. Murri [34] also describes changes in the peripheral nerves and in the intramuscular end-plates. One of us (I. S.) had occasion to examine the nervous system histologically in the case reported by Mandelbaum and Celler; [54] we found the medullated nerve fibers as well as the sensory nerve endings, "muscle spindles," absolutely free from pathologic changes; the same was true of the brain and cord except for a small lymphorrhage in the medulla, the first of its kind reported; but the nerve tissue near that infiltration was intact. Buzzard also found in one of his cases small lymphorrhages between the cells of some of the ganglia of the posterior nerve roots, but he does not mention the effects of these infiltrates on the nerve structure. Mott and Barrada [74] found in one case a general diminution of the basophilic substance throughout the central nervous system; this was most marked in the small and large cells of the thalamus and was associated with vacuolization, eccentric nuclei, satellite cells and increased neuroglia; the oculomotor nucleus showed similar though less marked changes, as

71. Guthrie, L. G.: Lancet **1**:393, 1901; **1**:330, 1903.

72. Leclerc and Sarvonat: Rev. de méd. Paris **25**:862, 1905.

73. Marinesco: Semaine med. **28**:421, 1908; Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1369 (Nov.) 1925.

74. Mott and Barrada: Brain **46**:237, 1923.

did the nucleus of the patheticus, though still less pronounced; the anterior horn cells in the spinal cord showed marked chromatolysis, eccentric nuclei and swollen vacuolated cytoplasm here and there. Widespread lipoid granules also were found in the perivascular spaces; this, in Mott and Barrada's opinion, proves that these lipoid changes occurred ante mortem. The cerebral cortex and the cerebellum showed similar but less marked changes. The terminations of the nerve fibrils within the muscles were intact. Lymphorrhages were not present in the central nervous system.

A review of the accessible literature fails to find reports of lesions of the central nervous system other than degenerative manifestations in the nerve cells such as chromatolysis, pigment formation, hemorrhages, etc. All these changes, however, are not of any significance as far as the pathogenesis of the disease is concerned, because: (1) they are not sufficiently constant; (2) mere cellular changes without reaction of the neuroglial tissue are difficult to harmonize pathologically with so typical and more or less constant a clinical disease picture as myasthenia gravis. By far the majority of patients thus far examined did not show lesions of the central or peripheral nervous system, at least not with the histologic methods in use at the present time. The changes that have been described, if not the result in some cases of faulty technic, are either agonal in nature or if present ante mortem are probably secondary, and perhaps are caused by the same pathogenic factor that is at the basis of the lymphorrhages, the muscular atrophies, and the metabolic changes.

THE ENDOCRINE GLANDS

Thymus.—As far as one can gather from the literature, some form of thymic involvement is found in nearly half the cases. Enlarged or persistent thymus in myasthenia gravis usually is described as showing a normal histologic structure, a tumor or a simple hyperplasia.

The study of thymic tumors had not led to unanimity of opinion until Ewing [75] and Bell [76] showed that they are essentially derivatives of embryonic thymic tissue. Ewing prefers to designate these tumors as "thymomata"—a term previously suggested by Grandhomme, Thiroloix and Debré [77] and Simmonds.[78] Ewing divides thymic tumors into two main groups: the first is lymphosarcoma or thymoma, composed of a diffuse growth of round, polyhedral and giant cells; the chief source of this tumor probably is the reticular cell, but abundant

75. Ewing, J.: Surg. Gynec. Obst. **22**:461, 1916.

76. Bell, E. T.: Am. J. Anat. **5**:29, 1905; J. Nerv. & Ment. Dis. **45**:130, 1917.

77. Grandhomme, Thiroloix and Debré: Arch. de méd. expér. et d'anat. path. **19**:668, 1907.

78. Simmonds, M.: Ztschr. f. Krebsforsch. **12**:280, 1912-1913.

lymphocytes often are present. The second group is composed of carcinomas arising from the reticulum cells. To these may be added a rare and somewhat questionable type of tumor attributed to the stroma and called spindle-cell sarcoma of myxosarcoma. Lymphosarcomas or thymomas are the most frequent of thymus tumors. They occupy the anterior mediastinum and usually extend from the sternal notch as high as the thyroid down to the diaphragm; they usually surround and compress the trachea, bronchi, pericardium, pleura and the large thoracic vessels; less often they invade these structures and metastasize into the spleen, liver, suprarenals, kidneys, pancreas, bones, marrow and brain. The symptoms produced depend a great deal on their location and size. They may produce death by either gradual or sudden asphyxia caused by compression of vital intrathoracic structures or by metastasizing into other organs.

The more rapidly growing tumors may be soft in consistency, but as a rule they are remarkably dense from diffuse fibrosis. The soft tumors may be vascular and hemorrhagic with areas of softening and cystic formations, which on section are found to contain a creamy, yellow or lemon colored fluid. The firmer growths usually are lobulated, with dense fibrous septums interspersed between the lobules. Some malignant growths showing microscopic changes have been found strictly encapsulated within the mediastinum. Ewing believes that all so-called spindle-cell sarcomas, endotheliomas and peritheliomas of the thymus are merely different varieties of thymoma.

Another less commonly encountered thymic tumor is thymic carcinoma. The gross anatomy of thymic carcinoma is identical with that of hard thymoma of the round cell type. Ewing points out that, although these tumors metastasize, they are less apt to invade surrounding organs and are less active in their growth than is usual with a distinctly carcinomatous tumor.

Thymic tumors occurring in myasthenia form a distinct group; they are all comparatively small benign growths, consisting, as stated before, of young thymic tissue. Most authorities seem to be general in their statements that these tumors are special forms of hyperplasia and not true neoplasms and therefore designate them as benign thymomas. The occurrence of lymphorrhages in the muscles and other organs in connection with these thymic tumors is believed by Ewing to favor the view that some thymic tumors are manifestations of an infectious granuloma.

If one is justified in drawing any conclusions as to the pathologic nature of a growth from the results of therapy, we would suggest that in our cases (H. B. and H. G.) the rapid disappearance of the mediastinal shadow following radiotherapy might be indicative that in both cases a thymic hyperplasia rather than a true neoplasm was present.

Several theories have been advanced in the attempt to explain the pathogenesis of myasthenia gravis. Its development in some instances after infectious diseases and intoxications, trauma and overexertion has led some authors to believe that it was the result of these causes.

Its constitutional character first was emphasized by Oppenheim,[26] who mentions its association with such degenerative phenomena as polydactylism, micrognatia, cleft-palate, infantilism, congenital ptosis, myotonia, syringomyelia, Friedreich's disease, facial hemiatrophy, and double central canal. The finding by Knoblauch, Buzzard and others of a preponderance of the light muscular fibers over the dark ones is believed by them to be evidence of some form of abiotrophy—a congenital predisposition to the disease. Marinesco,[73] after finding the disease in two sisters, speaks of its hereditary character. This association recently has been pointed out by Hase also, who found the disease in the family with numerous stigmas of degeneracy, partly endocrine and partly nervous in nature.

Other Glands.—In myasthenia gravis, as in other diseases of unknown etiology in which the functional disturbances cannot be explained on the basis of the pathologic lesions found, great stress has been laid on dysfunction of the endocrine system as the chief pathogenic factor. Its association in many instances with pregnancy, its coexistence with scleroderma, addisonian and basedowian syndromes, the finding in one case of an adenoma of the hypophysis, and the frequent occurrence of some form of pathologic change of the thymus, as well as the ability to produce experimentally in dogs the myasthenic reaction after the injection of pancreatic extract, are, in the opinion of some, indicative that the disease is due to endocrine disturbances. Curschmann,[18] in commenting on the lack of parallelism between the clinical and pathologic phenomena of the muscles, states that, because of the frequent coexistence of endocrine symptoms in myasthenia, it is difficult to decide whether this disease is a distinct clinical entity or merely a symptom of endocrine dysfunction. He is inclined to base the cause of myasthenia on a definite disturbance of a functional correlation of the endocrine glands, which, after an initial latency, appears in the thirties or forties. How far other exogenous causes act as exciting factors Curschmann does not know. Orzechowsky and Stern believe that the disease is not caused by a dysfunction of any one endocrine gland but by a faulty interrelation of all endocrine glands. The endocrine theory is supported by the claims of Lundborg as well as those of Chvostek,[79] who attribute the condition to a hypofunction of the parathyroids. These authors base their hypothesis on the assumption that both tetany and myasthenia affect the neuromuscular apparatus

79. Chvostek: Wien. klin. Wchnschr. **21**:37, 1908.

but are diametrically opposite in their clinical manifestations, and that since tetany is the result of a hyposecretion of the parathyroids, myasthenia must be the result of a hypersecretion of these bodies. Marinesco reports two cases of myasthenia which he attributes to disturbances of the vegetative nervous system of suprarenal origin. Reduced formation of substances controlling the vascular tonus is held to be responsible for the inverted vasomotor reaction consisting of dilatation of the vessels during voluntary muscular contractions. This, Marinesco believes, probably affects the acid-base balance of the muscle fibers, stimulating the production of hydrolytic and lipolytic ferments, which gives rise to lesions in the muscles. Parhon [80] again attaches significance to the fact that during the performance of the Abderhalden test he found a breaking down of muscle, thymus and parathyroid. Klose and Vogt found rapid exhaustion of the muscles in dogs following thymectomy. Müller could effect normal fatigue by injecting thymus extracts; in some cases the muscular contractions increased after these injections, and in others the contraction curves declined slower than normally. The persistence of a thymus or the presence of thymus hyperplasia in some cases of exophthalmic goiter and the effect of thymectomy in animals on the function of the suprarenals and chromaffin system with the general syndrome of asthenia following disease of the latter constitute additional evidence in the opinion of those who support the endocrine theory of myasthenia gravis.

As far as the relationship of the thymus to this disease is concerned, we wish to point out that, thus far, all the available evidence from extirpation experiments fails to prove that the thymus has any endocrine function. As a matter of fact the latest investigations by Hamman, Pappenheim, Park and McClure, and others would seem to show that, in animals at least, the thymus is not essential to life. There is good reason to believe that it is a hemopoietic organ. The small thymic cells are certainly lymphocytes and these, as Danchakoff has shown, possess the power of giving rise to plasma cells and polymorphonuclear leukocytes; the formation of red blood cells, if it occurs at all in this gland, probably is restricted to the embryo. It would seem that in all probability the thymus is of significance in the physiologic and pathologic processes merely by virtue of its lymphoid character. Whatever function it has is probably concerned with the defensive mechanisms of the body against infection.

Persistent thymus found accidentally at post mortem in persons who during life did not present any evidences whatever of myasthenia is common; and, on the other hand, as far as one can gather from statistics, only 55 per cent of the cases of myasthenia gravis show any

80. Parhon, C. J.: Compt. rend. Soc. de Biol. **76**:663, 1914.

kind of pathologic change in the thymus at necropsy. Recently, Greenfield has pointed out that negative observations in regard to the thymus are of little value unless the mediastinum has been searched carefully and systematically, since thymus tissue can be readily overlooked in the fat of this region; but even he adds that "it is difficult to state whether the thymic changes in myasthenia are primary or secondary to disease of some of the other endocrine glands."

The danger of drawing definite conclusions from animal experiments as to the relation of some endocrine glands to certain diseases is well illustrated by recently reported experiments. Eddy,[81] in an attempt to determine whether an excess of the product of thymus activity in the circulating blood caused exophthalmic goiter, injected hypodermically into three rabbits (two controls) thymus substance in the proportion of 5 mg. per kilogram of body weight, and into three rabbits, 10 mg. per kilogram of weight. Each rabbit received forty injections. Evidence of the production of exophthalmic goiter was not present in either group of rabbits. Bircher,[82] on the other hand, was able to induce a complete picture of exophthalmic goiter in three dogs and a partial picture in three other dogs by transplantation of thymus, "thus," he says, "proving the possibility of the thymogenous causation of exophthalmic goiter."

We have, we believe, presented abundant evidence that, in spite of the admitted presence of pathologic change of the thymus in more than half the cases of myasthenia gravis, the endocrine theory as to the causation of this disease does not rest on sound scientific ground. Many authors also have attempted to link the metabolic disturbances noted in many cases of the disease with the endocrine disturbances, attributing its pathogenesis to both of these factors. The great lack of uniformity in the results reported from metabolic studies in myasthenia gravis and the entire absence of metabolic disorders in many cases seem to us ample evidence, even if it is only negative in nature, that metabolic disorders cannot be seriously regarded as the primary cause of myasthenia gravis. We are willing to admit that both the endocrine disturbances and the metabolic disorders play a significant rôle in the clinical manifestations of the disease, but we are more inclined to regard them as the effects rather than the cause.

THE MYASTHENIC REACTION

A satisfactory explanation has not as yet been offered as to the nature of the myasthenic reaction. As a matter of fact, it still remains unsettled whether the cause of the reaction is myogenic or neurogenic.

81. Eddy, N. B.: Canad. M. A. J. **9**:203, 1919.

82. Bircher, E.: Schweiz. Arch. f. Neurol. u. Psychiat. **8**:208, 1921

Gowers believes that it is myogenic in origin. Kolischer, Widal and Marinesco,[73] Murri,[84] Guthrie,[71] Leclerc and Savornat,[72] and Mott and Barrada [74] believe that they find sufficient anatomic evidence in the central nervous system to justify a correlation between the changes in the latter and the manifestations of myasthenia. Grocco, Flora and Albertoni [29] believe that the reaction is neurogenic in origin. Goldflam [5] considers it cortical, and Salmon [50] attributes the phenomenon to a functional fatigue of the cortical sensory centers. Gordon Holmes,[83] on the other hand, argues against a neurogenic pathogenesis, because in myasthenia there is an involvement of individual muscles, whereas cerebral disturbances lead to a disturbance of movement and not of function of individual muscles.

The myasthenic reaction is merely a fatigue reaction, i. e., a more or less complete loss of irritability and contractility of muscle brought on by functional activity; an interval of rest, varying in duration, ordinarily is sufficient to bring about the return of irritability and contractility.

Because of the fact that the reaction can be obtained on direct stimulation of the muscles, Lewandowsky [24] believes that the cause of the reaction must be sought in the muscle fibers and not in the nerve endings. He suggests two possibilities: (1) A toxic effect, a toxin circulating in the blood which paralyzes the muscle, or an accumulation in the blood of fatigue products which inhibit further muscular contraction; (2) a change in the muscle chemistry in consequence of which the substance that is the immediate source of muscular contraction either ceases to be stored in the muscle, or, if present, is too quickly used up, so that further contraction becomes impossible.

Jolly,[33] in his original description of the myasthenic reaction, expresses his belief that the direct cause is a chemical change in the muscle substance, but that this chemical change is remotely influenced by certain processes in the central nervous system. In this connection he cites Mosso who assumes that, in this disease, cerebral activity gives rise to certain abnormal metabolic products which find their way into the circulation and thus produce chemical changes in the muscles. Jolly points out that the myasthenic reaction is the direct opposite of the myotonic reaction, in the sense that when a patient with myotonia innervates his muscles the latter remain in tonic contraction much longer than the patient desires, in consequence of which execution of movement becomes impossible; if he waits a short period the muscle becomes somewhat exhausted (Jolly), and then first the desired movement can be carried out normally, i. e., with a renewal of a fresh stimulus, the tonicity or the contraction of the muscle is diminished,

83. Holmes, Gordon: Brain **46**:279, 1923.

so that after repeated contractions the muscle responds normally to voluntary stimuli. In myotonia too, not only volitional stimulation but also tetanic electric stimulation gives rise to an abnormal reaction, which, with the continuation of the stimulus, becomes less and less marked and eventually becomes normal. This phenomenon, according to Jolly, also is to be attributed to a change in muscle chemistry, which, in myasthenia, must be directly opposite in nature to that of myotonia.

Investigations of normal muscle with action currents by Piper [84] have shown that, during fatigue, the frequency of the diphasic waves dropped from 50 to 25 or 30, i. e., all impulses transmitted from the nerve did not reach the muscle; from this Piper deduces that fatigue of a normal muscle begins with a diminution of the nerve impulse, so that the nervous system must participate in the phenomenon of fatigue. Electromyographic studies of myasthenic muscles, carried out by Herzog,[85] yielded curves similar to those obtained from normal non-fatigued muscles when the latter were innervated only feebly. In myasthenic muscle, however, the onset of fatigue was characterized by a diminution in the amplitude of the wave, though the number of waves per second remained unchanged. Herzog obtained 50 diphasic waves per second in a recuperated myasthenic muscle with the string galvanometer, which resembled in every respect recuperated normal muscle except that the myasthenic muscle developed less power. Fatigued myasthenic muscle, on the other hand, showed an entirely different condition from fatigued healthy muscle, because, although the frequency of contracting waves remained at 50 (even during exhaustion), the amplitude of each individual wave was diminished considerably. This shows that myasthenic fatigue is absolutely different from fatigue of normal, healthy muscle. The conduction of the impulse, the reflex period and the innervation remained unaltered in these investigations. Therefore, changes did not take place in the function of the nerves, so that Herzog concludes that the cause of the fatigue in myasthenia cannot be referred to the nervous system. Schäffer and Brieger [86] recently studied muscle action currents in a case of myasthenia gravis and obtained curves identical with those obtained by Herzog; they admit, however, that, although their experiments also would seem to point to the muscles as the site of origin of the myasthenic reaction, nevertheless participation of the nervous system in the mechanism cannot be excluded. These authors also found that the fatigue induced in myasthenic muscles by voluntary contractions is entirely different from that induced by voluntary contractions of normal muscle. Whether this is due to a

84. Piper: Electrophysiology of Human Muscle, Berlin, Julius Springer, 1912.
85. Herzog: Deutsches Arch. f. klin. Med. **123**:76, 1917.
86. Schäffer and Brieger: Deutsches Arch. f. klin. Med. **138**:28, 1922.

functional disturbance, to a degeneration of the muscles, or to a change in innervation they are unable to state.

The fact that in the myasthenic reaction the muscle reacts well to galvanism after complete exhaustion to faradism is, in the opinion of many, at least suggestive that the causation of the fatigue is not limited to muscle. From the results of ergographic studies in myasthenic muscle, Symmonds [87] believes that there is sufficient justification for assuming a lesion in the nervous mechanism of movement to explain the fatigue reaction in this disease. He emphasizes the occasional presence of pains and other sensory symptoms as evidences of involvement of the nerves; we already have stated that we do not believe that the pain and sensory symptoms occasionally encountered are significant in indicating nervous involvement.

The divergent views mentioned above on the part of so many competent observers are, in our opinion, readily reconcilable when we take into consideration the recent work by Boeke,[88] who has shown that the periterminal network is intimately connected with the functions of the neurofibrillar structure of the motor endings. As the neurofibrils are the actual conductors of the nerve impulses, it is assumed that, the neurofibrillar structure not being continuous with the contracting substance of the muscle fiber, the impulse is carried on by the periterminal network and in this way transmitted to the contracting substance of the muscle fiber, the myofibrils. Langley believes that in the case of a connection of the peripheral end of an efferent nerve with a cell one or more substances (Langley's receptive substances) capable of receiving and transmitting stimuli and capable of isolated paralysis must be present. According to Langley, it is this substance which is stimulated or paralyzed by poisons ordinarily regarded as stimulating or paralyzing nerve endings. Probably not only the function of reacting to numerous chemical bodies but also the special liability of both afferent and efferent nerves to fatigue must be transferred from the nerve endings to the same constituent of the cell. The nerve ending itself is, according to Langley, not essentially different from the nerve fiber. The general opinion of physiologists now is that a morphologic substratum of the receptive substances is not to be looked for in histologic preparations. Yet the later work of Langley and that of Keith Lucas on the different behavior of the neural region of the muscle fiber and the aneural region as regards the action of poisons lend support to the view that such a substance exists in the proximity of the nerve endings in muscle. From all these facts Boeke concludes that one may look for a well-defined,

87. Symmonds: Brain **46**:279, 1923.

88. Boeke: Brain **44**:1, 1921.

sharply localized morphologic basis for this receptive substance inside the sarcoplasm between the nerve ending and the contractile substance. We believe that it is probably at this point, i. e., at the periterminal network, that the chemical phenomena of fatigue occur as a result of the effect of whatever toxin or toxins are circulating in the sarcoplasm.

The myasthenic reaction also may bear some relation to muscle tonus. The failure of a contracting muscle to contract to further stimulation, with prompt recovery after a short period of rest and a renewal of the original contraction, must be associated with changes in muscle posture, the regulation of which may have something to do with the neural mechanism of tonus. In the present state of knowledge it is possible that this mechanism may reside in the sympathetic nervous system. If Boeke's conception that there is dual innervation of striated muscle and that the peripheral terminations of sympathetic nerves in striated muscle is an anatomic fact as well established as that of their termination in nonstriated muscle is correct, it would lend support to this hypothesis. There is also anatomic clinical evidence that the higher centers regulating the sympathetic nervous system are represented in the midbrain, especially the hypothalamic region; bearing this in mind with the fact that lesions in this region (as observed in epidemic encephalitis) give rise to a syndrome simulating that of myasthenia gravis would, in our opinion, be additional evidence in support of the theory that changes in tonus must be of great significance in the production of the myasthenic reaction.

From what has been said thus far it can readily be seen that the peripheral site of origin of the myasthenic reaction is most likely the periterminal network. We are not as yet in possession of anatomic evidence to substantiate this hypothesis, because, as far as we can gather, not any case of myasthenia gravis has been subjected to the more recent histologic methods of examination necessary to study the periterminal network. Should such anatomic changes not be demonstrated in the future, this hypothesis would not necessarily fail, because it is well known that there are many diseases, especially of the neuromuscular system, which intra vitam present the grossest manifestations of disturbance of function, whose underlying cause cannot at present be demonstrated morphologically.

We also know that active chemical changes take place in the neuromuscular system during contraction, rest and fatigue; these biochemic changes involve processes of hydrolysis, of oxidation, of reaction and of synthesis; they are affected by various enzymes, alkaloids, endocrine secretions, hormones and toxins. There is not as yet any uniformity of opinion among physiologists as to the special nature of the chemical phenomena that are at the basis of fatigue in normal muscles. The

generally accepted view is that the products of muscular activity, if allowed to accumulate in muscle, diminish or suppress its contractility, and that in all probability, this effect is the result of the acidity of the products formed (lactic acid, carbon dioxide). It is possible, of course, that other intermediary substances are produced which may have a similar effect. Weichardt,[89] for instance, said that he had isolated a fatigue toxin (kenotoxin) which, when injected into the circulation of a fresh animal, brings on fatigue or even death. When it is injected in suitable doses the body may form an antitoxin, which when given to another fresh animal will prevent fatigue. This work, however, has not been corroborated, and, according to Howell, all that one can say today is that in all probability the loss of power to do work is referable in part to a using up of the supply of energy-yielding material, but that the accumulation of acid fatigue substances is doubtless the immediate cause of fatigue. How far these principles of fatigue in normal muscle can be made applicable to fatigue in myasthenic muscle which, as we have shown, functions so differently from normal muscle, is a question that can be decided only by an experimental reproduction of the myasthenic reaction or by the finding of chemical differences in myasthenic muscle. Supported only by clinical and anatomic facts—inconstant as the latter are—the only rational conclusion that the clinician can draw is that myasthenia gravis is a disease characterized by a functional disturbance in the nature of a peculiar muscular fatigue induced by some unknown endogenous poison or poisons with a peculiar selective affinity for the muscles and their motor and sympathetic (?) nerve endings, as well as for the lymphatic component of the hemopoietic system (lymphorrhages) and for the endocrine system, especially the thymus.

Course, Duration and Prognosis.—The onset of myasthenia gravis in most cases is gradual; however, it may be sudden. It usually begins in the ocular or bulbar muscles, but it may begin in the muscles of the extremities and involve the bulbar and ocular muscles later. Hun, Blumer and Streeter [15] found that in 40 per cent of the cases the disease began in the ocular muscles, and in 30 per cent in the muscles of the extremities. Karplus reports a case in which the involvement was limited to the ocular muscles for twenty years, after which it extended to the trunk and limbs. In McKendree's [40] case, sixteen years elapsed between the appearance of the ocular symptoms and the symptoms referable to the throat and jaw; during this time, the patient was in a low state of vitality but was able to manage her household and gave normal birth to three normal children. Curschmann [18] reports a case

89. Weichardt, W.: München. med. Wchnschr. **53**:135, 1906; Med. Klin. **2**: 1151, 1906.

in which the relatively harmless stage lasted twenty-two years. In Stiefel's [9] case the disease was limited to the ocular muscles for one year, after which it extended rapidly to the jaw and throat muscles, finally involving the rest of the body.

The further progress of the disease may be acute or chronic and relapsing. Widal and Marinesco [73] report one case which lasted only fourteen days, and Dorendorf saw one terminate fatally in twenty-nine days. Early in its course all symptoms may disappear for days, weeks, months and years. Remissions are so common that they are regarded as a characteristic feature of the disease. Exacerbations with or without aggravation of symptoms may follow trauma, exertion, infectious diseases, especially tuberculosis (Widal and Marinesco), and pregnancy. As the disease advances the remissions become shorter and shorter. The course varies greatly according to the severity of the individual symptoms. In the final stages the myasthenia persists or shows only slight changes according to the condition of rest and fatigue; the patients become bedridden; nutrition suffers greatly through involvement of the muscles of chewing and swallowing, and sooner or later attacks of dyspnea due to involvement of the respiratory muscles make their appearance. It is during one of these attacks that death usually occurs from respiratory or cardiac paralysis. Sudden death also may occur from asphyxia, due to choking, or after an effort that strains the heart (passing a stomach tube [Oppenheim], hot baths, etc.); in most cases, however, death is caused by an aspiration pneumonia, or by complications.

The prognosis is extremely grave. Improvement and recovery, though not impossible, are rare. The cases with a predominance of ocular symptoms offer the best prognosis as regards life. One of our patients has remained symptom-free for eight years, and another is well subjectively after two and one-half years, although her muscles still show the presence of the myasthenic reaction. The most severe symptoms of myasthenia may disappear, but after a period of apparently good health they may reappear suddenly and lead rapidly to a fatal termination.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

There is not, as a rule, any difficulty in the diagnosis of a typical case of myasthenia gravis when one bears in mind that the disease is characterized by: (1) the early appearance of weakness—not a genuine paralysis— of the levator palpebrae, orbicularis oculi and the muscles of chewing, swallowing and speech and of the muscles of the back and later of the trunk and extermities; (2) the absence of muscular atrophy; (3) the absence of the reaction of degeneration; (4) the presence of

general weakness following exertion; (5) the presence of the myasthenic reaction to tetanization by the faradic current and to repeated mechanical and prolonged volitional stimuli; (6) the rapid recuperation from fatigue of the involved muscles following a short period of rest; (7) the presence of lymphorrhages in a piece of excised muscle; (8) the findings in the roentgenogram of a shadow in the mediastinum, in the region of the thymus.

Early in the disease myasthenia gravis may simulate hysteria or neurasthenia. The type of weakness of the ocular muscles, the dysmasesia, the remittent character of the myasthenia and the presence of the myasthenic reaction will point to the diagnosis of myasthenia gravis. The coexistence of myasthenia gravis and hysteria will, of course, make an early diagnosis extremely difficult.

It is differentiated from polyneuritis by the absence of the usual subjective and objective sensory disturbances and by the absence of muscular atrophies and of reflex and electric changes. Loss of accommodation or absent knee jerks in a patient with a history of a recent attack of diphtheria will be in favor of postdiphtheritic paralysis rather than of myasthenia gravis. Differentiation from a polyneuritis involving the bulbar nerves is much more difficult, especially at the beginning. The same difficulty may be encountered in syphilis involving the bulb and in the acute form of Landry's paralysis, particularly when the latter begins in the muscles innervated by the bulbar nerves and which may terminate fatally before the extremities have been affected.

Myasthenia gravis is distinguished from the muscular dystrophies and atrophies by the absence of typically distributed pseudohypertrophies and atrophies, by the presence of remissions, by a different type of progression, as well as by the presence of the myasthenic reaction without any reaction of degeneration, by the rapid recuperation of the muscle weakness after a short period of rest, and by the finding of a thymic shadow; if the diagnosis is doubtful, the finding of lymphorrhages at biopsy will be conclusive.

It may be extremely difficult to differentiate between myasthenia gravis and chronic polio-encephalomyelitis. The atrophy of the muscles involved, with a diminution or loss of electric excitability, the absence of the myasthenic reaction, the absence of remissions, and the absence of lymphorrhages and of a thymic shadow will speak in favor of polio-encephalomyelitis.

In the absence of internal ophthalmoplegia, basal ganglion symptoms (parkinsonism, chorea) and lethargy, an epidemic encephalitis (lethargica) localized to the bulb may be indistinguishable from an early myasthenia gravis. The absence of remissions in doubtful cases will not be conclusive against a diagnosis of epidemic encephalitis;

we repeatedly have observed complete remissions of varying duration in the so-called myasthenic form of bulbar epidemic encephalitis. In this differentiation one will have to depend largely on the different type of muscle weakness, finding the myasthenic reaction, the results of biopsy, and roentgenographic studies of the mediastinum. The results of examinations of the spinal fluid, if negative, will not be conclusive either way.

Myasthenia gravis is distinguished from bulbar paralysis due to degenerative lesions of the bulbar nuclei (glossolabiolaryngeal paralysis) by the presence in the latter of a true paralysis, atrophy, fibrillations (of the tongue especially) and reactions of degeneration in the muscles involved, by the absence of remissions, by negative biopsy and roentgenographic examinations and by its progressive and rapidly fatal course.

A history of cerebral arteriosclerosis with repeated attacks of apoplexy with the signs of bilateral paralysis of the upper motor neurons (spasticity, increased tendon reflexes, absent or diminished abdominal reflexes, pathologic reflexes) and the presence of mental symptoms and sphincteric disturbances will be sufficient to distinguish pseudobulbar paralysis from myasthenia gravis. These criteria, except for the previous history and mode of onset, also can be utilized in differentiating myasthenia from neoplastic and aneurysmal lesions localized in the posterior cranial fossa. Toxic conditions, in which bulbar symptoms due to poisoning (typhoid, fish, botulism and barium salts) are a predominating feature in the clinical picture may, on superficial examination, closely resemble myasthenia gravis. Here, of course, the history, the laboratory examinations and the progress of the disease will have to be taken into consideration before a definite diagnosis can be made.

The differentiation from the nuclear aplasias and hypoplasias is comparatively easy when it is remembered that these conditions are congenital and, as a rule, nonprogressive. In this connection, however, it is well to bear in mind that these congenital nuclear conditions frequently are found in myasthenia gravis, and are even regarded by some observers as predisposing factors in the disease.

There cannot be any difficulty in distinguishing between myasthenia gravis and Gerlier's disease (*vertige paralysant*). In the latter, the muscles of chewing and the facial muscles (except the levator palpebrae superior) are affected rarely, the extensors of the limbs are more commonly affected than the flexors, and severe vertigo and visual disturbances accompany or precede the myasthenia. Gerlier's disease appears in attacks that may last only a few minutes and occur from ten to twenty times a day. It has thus far been reported only in Switzerland and in Japan; it appears in the warm months and disappears with the onset of cold weather.

The mode of onset, the presence of signs of involvement of the pyramidal or extrapyramidal system or both, the absence of myasthenia (though not necessarily of the myasthenic reaction), and the absence of remissions will be sufficient to differentiate the cerebral diplegias from myasthenia gravis.

TREATMENT

Before discussing the treatment of myasthenia gravis, we desire to emphasize the importance of subjecting every beneficial therapeutic result reported by others or obtained by oneself to a careful critical analysis. As in any other chronic disease of unknown etiology in which spontaneous remissions are a characteristic feature, so in myasthenia gravis must any result obtained from therapy be scrutinized and final judgment as to its efficacy held in abeyance, in case a remission should be interpreted as a cure. Another factor constantly to be borne in mind in a problem of this sort is the psychic state of a patient affected with a chronic painless disease of long duration, the principal symptoms of which are weakness and disturbances of function that disappear after a short period of rest to return with any renewed effort at activity. Every clinician is well acquainted with the ease with which such patients react to any form of suggestion. This abnormal suggestibility must be taken into consideration in the evaluation of the results of therapy, especially if one attempts to utilize the alleviation of subjective complaints as a therapeutic guide.

The most important therapeutic requisite is the insistence on complete physical and mental rest. The patient is to be kept in bed in a well-ventilated room, preferably with a southern exposure, for weeks and months with a hope that a remission may set in. The next important problem is that of feeding a patient having a disease in which the danger of suffocation is as great as in myasthenia gravis. Monrad-Krohn [90] points out how the myasthenic reaction can be given practical application in the treatment, and particularly in the feeding of the patient. He suggests that a nurse always should be present and should see that when the patient takes a mouthful of food a sufficient interval has elapsed before the next mouthful is given; this gives the muscles concerned in chewing and swallowing an opportunity to recover from the fatigue after each effort. The question as to whether the food given should be solid or liquid will depend on whether chewing induces fatigue. The patient is to be spoonfed and is not to drink out af a glass or cup. If ordinary feeding by mouth is insufficient, rectal feeding and rectal administration of glucose are advisable. In a dangerous case gavage might be employed, but with a realization of the dangerous

90. Monrad-Krohn: Norsk. Mag. f. Laegevidensk. **79**:489, 1918.

nature of such a procedure in this disease. Bruns warns against the use of anesthetics and narcotics in these patients. From the nature of the disease it would seem that all forms of exercise, massage, gymnastics, baths and faradism are not only useless but actually are contraindicated. Erb was the first to employ central galvanization, and some authors have, since then, reported good results from applications of the galvanic current to the muscles; with this method too, however, repetition of muscular contractions must be avoided.

As in all debilitating diseases, tonics such as arsenic, phosphorus, quinine and iron are employed. It is self-evident that in a disease in which absolute rest is of such importance as in myasthenia gravis any drug that exerts a stimulating effect on the muscles, such as strychnine, would seem to be contraindicated. Yet in spite of this seemingly rational contraindication, case after case has been recorded in which good results are reported from the use of this drug. Only recently, Dana [91] has reported good results following enormous doses of strychnine (from 1 to 3 grains [0.065 to 0.195 Gm.] three times a day). Still more recently, Jackson and Bates [92] have reported early improvement in a patient who was given strychnine in increasing doses until he received as much as from 1 to 4 grains (0.065 to 0.260 Gm.) four times a day. We have used injections of strychnine in much smaller doses in our cases, but we do not know whether the improvement noted was the result of strychnine or of the absolute rest that we subjected our patients to, or whether the apparent improvement was merely a remission.

The conception that the disease was caused primarily by metabolic disturbances led various investigators to subject their patients to various forms of dietetic therapy. Thus, Murri [34] increased the daily carbohydrate intake, without effect. Pemberton [64] recommended the administration of calcium in order to supply the calcium deficiency. Diller and Rosenbloom [62] entertained the possibility that the lack of utilization of the calcium-ion in this disease interferes with the normal endogenous metabolism, and with this view in mind they subjected one of their patients to calcium therapy, with good results, they say. The idea that the protein metabolism was at fault led Kaufmann to increase the albumin content in the diet. In view of what we said of the metabolic disturbances in discussing the symptomatology and pathogenesis, it is needless for us to comment further on this form of therapy.

The idea that endocrine disturbances are at the basis of the disease has led many to resort to opotherapy. Landouzy treated a patient with

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91. Dana, C. L.: Myasthenia Gravis, J. A. M. A. **78**:261 (Jan. 28) 1922.

92. Jackson, A. S., and Bates, A. D.: Myasthenia Gravis, J. A. M. A. **81**:114 (July 14) 1923.

suprarenal powder for fourteen days; at first he noted slight improvement, but this was soon followed by an aggravation of the symptoms. Buzzard and Lewandowsky failed to see any beneficial results from the use of suprarenal substance, whereas Calude and Vincent saw improvement following the use of this drug. Marie, Bouttier and Bertrand [93] report a necropsy in a case of myasthenia gravis in which the patient previously had been reported by them as permanently improved by suprarenal extract; the necropsy showed the nervous system to be intact, but they found small lymphorrhages scattered throughout the muscles and the suprarenals; they attribute the improvement following treatment by suprarenal extract to the lesions found in the suprarenals: "The improvement," they say, "lasted for six months, when the patient died of pulmonary edema." Tietz [94] describes a case in which epinephrine relieved the symptoms; the patient, however, died from erysipelas; necropsy revealed an abnormal structure of the cortex of both suprarenals and an adenoma in the medulla of one of them. Bookman and Epstein [55] did not obtain results from suprarenal, thymus, ovarian and testicular extracts. One of our patients (S. S.) is well after eight years; he was treated with thymus and strychnine hypodermically, and absolute rest. Raymond,[95] Buzzard [3] and others employed thyroidin; the results were disappointing, and Lewandowsky [24] is certain that one of his patients was made worse after the use of this drug. Preparations of hypophysial and ovarian glands were given by Delille and Vincent with excellent results, they say. Heald and Wilson [96] treated a man, aged 43, with strychnine and pituitary, but they say that they obtained "most beneficial results from absolute rest and the avoidance of fatigue." Kaufmann [60] employed, apparently with success, spermin on the advice of Harnack, in order to obviate the "alleged" disturbance of oxidation which the latter believes to be at the basis of the disease. He injects subcutaneously a double salt of spermin and sodium chloride (1 cc. of a 2 per cent solution) daily or every other day, as a palliative measure. Weichardt's fatigue toxin was employed by Oppenheim and by Görner without any beneficial results but on the contrary with an aggravation of the symptoms, whereas Rautenberg [30] reports transitory improvement.

Injections of thorium were used with good results by Falta, Kaiser and Zehner in lymphoma, and by Czerni and Caan in malignant lymph tumors and by Hirschfeld in lymphgranuloma. In view of this, and

93. Marie, Bouttier and Bertrand: Ann. de méd. **10**:173, 1921.

94. Tietz: Berl. klin. Wchnschr. **3**:1862, 1924.

95. Raymond and Sicard: Rev. neurol. **13**:120, 1905. Raymond and Lejonne (footnote **51**).

96. Heald, S. I., and Wilson, A. J.: Brit. M. J. **1**:852, 1923.

because of the possibility of the presence of a thymic tumor in his case, Stiefel [9] administered intravenously to his patient 1,000 and later 1,500 electrostatic units of thorium X; the first injection was followed by a marked drop in the leukocytes, and the second by a somewhat smaller drop. It did not have any effect on the myasthenia. These observations coincide with those of Silva and of Marello.

After Schumacher [97] saw improvement in a case of myasthenia gravis following thymectomy, Curschmann was led to employ roentgenotherapy in cases of this disease in which the roentgenograms showed a shadow in the region of the thymus. The rationale of this form of therapy apparently was based on the previous treatment of mediastinal tumors with roentgen rays by Kienböck, and von Elischer and Engel.[98] Pierchalla [99] subjected a patient, aged 48, who was suffering from myasthenia gravis and in whom all other methods of treatment were ineffectual, to roentgenotherapy. On March 12, April 6 and May 26, 1920, the woman received 300 Fürstman units on the left, right and anterior regions of the thymus, and "cross-fire" on June 6. After this, further treatment had to be stopped because of the onset of an erythema at the site of exposure. At this time, however, the general weakness and the myasthenia of the arm and leg as well as the ptosis and diplopia had entirely disappeared. On December 20 of the same year, reexamination showed that the patient was free from all symptoms and signs including the myasthenic reaction and had resumed her occupation as a telegrapher. Pierchalla points out that except for a hyperplasia of the thymus this patient did not show any evidence of endocrine involvement. He adds: "One would be justified to attribute the improvement to the roentgen-ray therapy were it not for the well recognized fact that in this disease frequent and prolonged remissions are known to occur after almost any form of treatment." Mella [100] reports improvement in two of his cases following irradiation of the thymus. Oppenheim, however, states that this measure always has failed him in myasthenia gravis. Our patients H. B. and H. G. also were subjected to roentgen-ray therapy with a resulting disappearance of the "thymus shadow" and a complete disappearance of symptoms. We are, of course, unable to state whether they are cured or whether they are merely going through a remission.[101]

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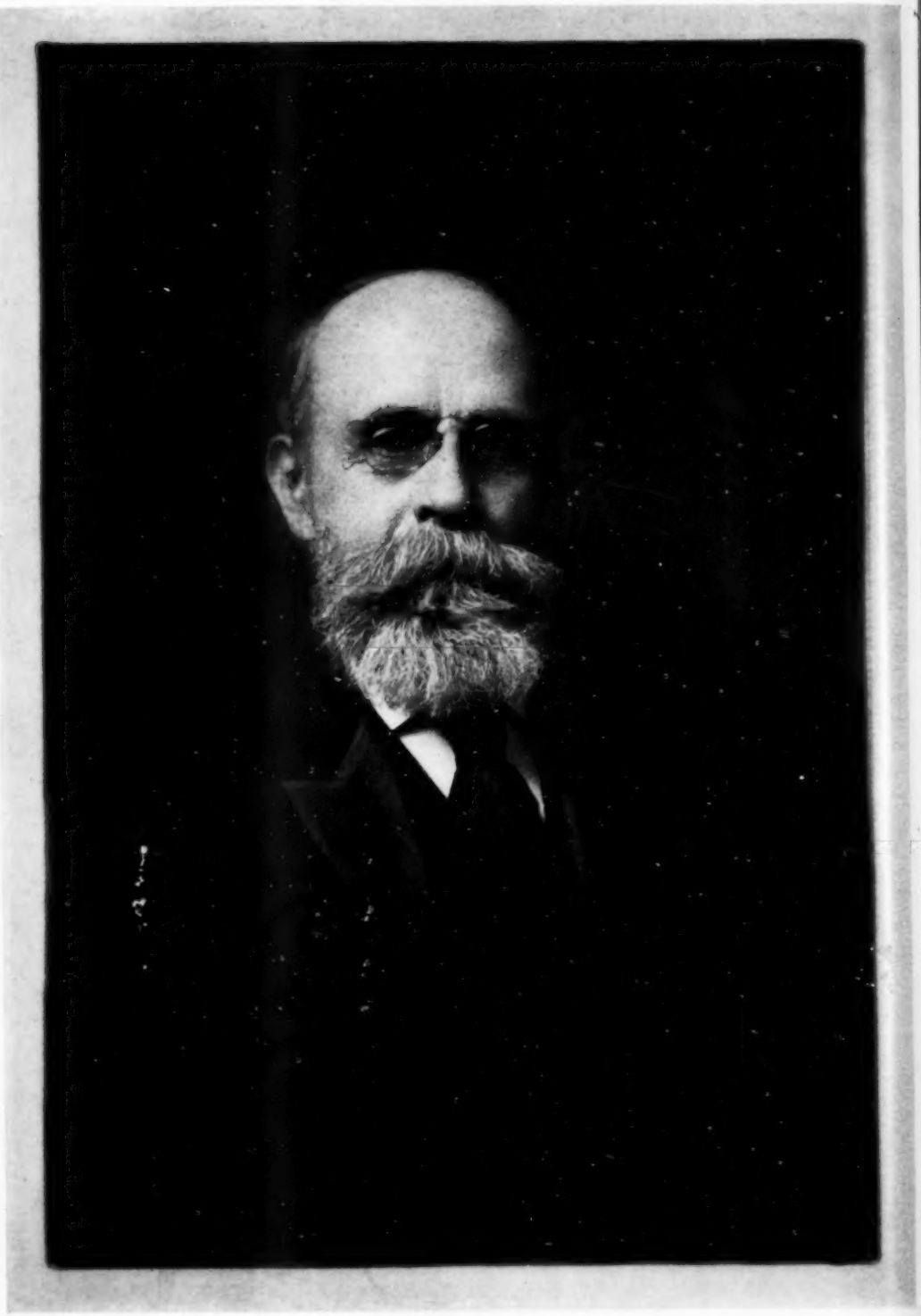
97. Schumacher and Roth: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**:746, 1913.

98. Von Elischer, J., and Engel, K.: Deutsche med. Wchnschr. **32**:1620, 1902.

99. Pierchalla: Therap. Halbmonatsh. **35**:504, 1921.

100. Mella, Hugo: M. Clin. N. Amer. **7**:939 (Nov.) 1923.

101. Details of the four cases studied, together with additional references to the literature, will be found in the author's reprints, copies of which will be furnished by them on request.



SAMUEL GILBERT WEBBER, M.D.
1838-1926

Obituary

SAMUEL GILBERT WEBBER, A.B., M.D.

1838-1926

In the death of Dr. Webber, American neurology loses one of its earliest exponents. He died, Dec. 5, 1926, at the age of 88, following a series of attacks covering a period of ten years, the result, no doubt, of arteriosclerosis. The final outcome was attributed to a massive cerebral hemorrhage preceded by a marked aphasia for three weeks before the end.

Dr. Webber came of old New England stock; his ancestors on the paternal side settled in Falmouth, Maine, whence they were driven by Indians in the early part of the seventeenth century, and sought refuge in the safer neighborhood of Boston. On his mother's side his forebears were merchants and lived in the fishing town of Gloucester, on the Massachusetts coast. Dr. Webber was born, July 24, 1838, in Boston, the son of Mr. and Mrs. Aaron D. Webber. His father was a carpenter and is said to have been the first of his calling to display a "carpenter and builder" sign to designate his place of business. The boy was prepared for college at the private Dixwell School, entered Harvard, and was graduated with the bachelor's degree in 1860, receiving his medical degree, likewise from Harvard, in 1865. His medical course was interrupted by the Civil War in which he served as assistant surgeon in the Union Navy from 1862 to 1865. This was considered for the degree that he received on the expiration of his service. The following two years he spent in medical study in Vienna, returning to Boston to enter on the practice of his profession.

He received the appointment of pathologist at the Boston City Hospital in 1869, and served for three years. He was also a physician at the Boston Dispensary, and visiting physician to the Carney Hospital from 1868 to 1870. His interest in the study of the nervous system began early, and to this subject he gave special attention at the Boston Dispensary until 1877. He was then made visiting physician to the now defunct department of nervous and renal diseases at the Boston City Hospital, which served in those early days to provide beds for patients having nervous disease—an unusual opportunity for study in this field, neglected for many years thereafter. This appointment continued for eight years and offered an opportunity for pioneer clinical and pathologic work. In 1885, Dr. Webber accepted the position of resident physician at the Adams Nervine, a privately endowed institution in Jamaica Plain, a suburb of Boston; his predecessor in that position

had been the late Dr. Frank W. Page. This entailed his resignation from the Boston City Hospital and also from the post of clinical instructor at the Harvard Medical School, to which he had been appointed in 1875. During his service at the Adams Nervine, which extended over a period of six years, his kindliness and skill found ample scope for their exercise, dealing as he did with patients largely of the psychoneurotic type. After his retirement from the active management of the Adams Nervine, in which he was succeeded by Dr. Robert T. Edes, he became one of its consulting physicians. On the opening of the Tufts College Medical School, he was appointed a member of its first faculty, with the title of professor of neurology. He continued to teach for the following ten years; at the end of that time he gave up all official appointments and finally, in 1917, at the age of 79, retired wholly from medical practice. The remaining years of his life were spent with his family in Newtonville, near Boston, where he devoted much time to the work of medical missions, in which he always had the keenest interest.

His society membership included the American Medical Association, the Massachusetts Medical Society, the Boston Society of Psychiatry and Neurology, and the American Neurological Association, of which he was made an honorary member on his retirement from active membership. He was a charter member of the latter society, and was the last but one of that distinguished group of thirty-five who sponsored this national organization, the first meeting of which was held in New York, June 2, 1875. It is also worthy of note that he read the first paper presented at this first meeting. Dr. Charles K. Mills, in his charming recollections of the early days of the association published in its semicentennial volume, has this to say of him:

> Samuel G. Webber, of Boston, was not only one of the charter members but had the honor of contributing the first scientific paper, in 1875, on myelitis. Webber was a New England type, earnest and conscientious in his work and ways. He wrote a small book on "Nervous Diseases," one of the first in this country. He frequently contributed to our proceedings by papers and discussions. He and Rockwell are the only charter members still living. Some years ago he was made an associate member. He was our original "total abstinence" member, a prohibitionist of half a century before the passage of the eighteenth amendment. He was never quite reconciled to the use of alcoholic beverages at our annual dinners.

In connection with the last statement, his daughter has informed me that his reason for not joining the Grand Army of the Republic and the Loyal Legion, to which his service in the Civil War had made him eligible, was his disapproval of the use of wine at their dinners and other functions. His convictions on this subject were fixed and irrevocable. He was an earnestly religious man in the common acceptation of that term. He was a life member of the Young Men's Christian

Association, the Massachusetts Home Missionary Society and the Boston Congregational Club. He thought at one time of entering the ministry, but is said to have decided that his service to humanity would be less efficient through the medium of the sermon than through ministration to the sick. His teaching was always tinged with the missionary spirit. He was for many years a trustee of the hospital for dipsomaniacs at Foxborough, Mass.

Dr. Webber's contributions to neurology were notable. His textbook, long out of print, is useful even in this late day and filled a decided need in its time. He wrote on a variety of subjects. In 1866 he was awarded the Boylston prize at the Harvard Medical School for an essay on cerebrospinal meningitis, and during the succeeding years, papers appeared on diseases of the peripheral nerves, lead paralysis, locomotor ataxia, pathologic histology of the spinal cord, epilepsy, syphilis and other subjects, largely dealing with the organic side of neurology. He was not a voluminous writer, but his work was thorough and painstaking, and may well repay a rereading in spite of newer knowledge.

For many years preceding his death he was seldom seen at medical meetings and took small part in medical affairs. He is remembered as a kindly and courteous man, retiring in disposition, serious minded and strict in his observance of what he considered right, a type of the old school, the passing of which we deplore. He married Miss Nancy Sturtevant, in 1864. A son, born in 1871, died the following year; his wife and two daughters, Maria Gilbert and Sarah Southworth Webber, survive him, and with them he spent the closing years of his long life. He had never been handicapped by illness except in later years and even then his natural vitality and alertness of mind, in spite of advancing cataracts and the natural inroads of age, made life well worth living up to a relatively short period before his death.

E. W. TAYLOR.

News and Comment

PARKINSON'S "ESSAY ON SHAKING PALSY"

Parkinson's "Essay on Shaking Palsy" is declared by Rowntree to constitute this English physician's greatest and most important contribution to medical literature. Garrison, in his "History of Medicine," refers to it as a unique and classic description of paralysis agitans, or Parkinson's disease. Ebstein recounts his unsuccessful efforts to obtain the loan of a copy from medical libraries in Europe.

Only five copies of the original edition (which was printed in London in 1817) are known to exist, three in Great Britain and two in America. Of these, one (a perfect example) is owned by the Surgeon General's Library in Washington, where it is carefully preserved under glass.

A plan for the reproduction in facsimile of type, paper and other details of the latter copy is now under consideration. If the plan is adopted it is proposed to offer a limited number of copies thus reproduced for sale at a price of $3.00, in library buckram, or of $5.00, in Turkey red morocco half leather.

It is believed that every neurologist will wish to avail himself of the opportunity to add a copy of the reproduction of this exceedingly rare and instructive work to his own library. Since the success of the undertaking will depend in large part on the patronage, it is hoped that the response will be generous. Orders may be addressed to Cary R. Sage, 5619 Western Avenue, Washington, D. C., and should be accompanied by an indication of the style of binding that is desired.

MISSOURI-KANSAS NEUROPSYCHIATRIC SOCIETY

The Missouri-Kansas Neuropsychiatric Society was organized at the University Club in Kansas City, Mo., on December 8. Twenty-five neuropsychiatrists from eastern Kansas and western Missouri were present. The program included a demonstration of cases of amaurotic family idiocy and of narcolepsy; a paper with lantern demonstration of cerebral fiber tracts exposed by gross dissection, and a talk on psychiatry in Europe from the internist's point of view.

Officers elected for the ensuing year were: president, Dr. Karl Menninger, Topeka; Dr. F. A. Carmichael, Osawatomie, vice-president; Dr. E. T. Gibson, Kansas City, secretary.

Abstracts from Current Literature

METHODS OF EXAMINATION OF THE SYMPATHETIC SYSTEM AND THEIR VALUE: ORGANIC DISEASE OF THE NERVOUS SYSTEM. A REPORT BEFORE THE SEVENTH RÉUNION NEUROLOGIQUE, PARIS, JUNE, 1926. ANDRÉ THOMAS, Rev. neurol. **1**:767, 1926.

The clinical examination of the sympathetic system has not progressed at the same rate as has that of the cerebrospinal system. In this respect, clinical medicine is falling behind the progress of the physiologists. It leaped ahead under the stimulus of the war and of various surgical operations performed on the sympathetic nerves, until at present the vision of Claude Bernard, of full information from a vast number of sources, may be regarded as a possibility. On account of this recent great extension of "vegetative pathology," the present report must be limited in scope. Terms have lost their value. Little by little the sympathetic system has taken the place of hysteria as a medical waste basket. The report deals strictly with the great sympathetic system first isolated by Willis in 1664. The autonomic system of Langley is not considered.

ANATOMY

The great sympathetic is the system that lies on each side of the vertebral column, running from the base of the skull to the coccyx. There are twelve ganglia in the thoracic region, three cervical (the second is inconstant) and five lumbar ganglia, from three to five sacral and one coccygeal ganglion closing the chain. From the superior cervical ganglion the carotid nerve follows the artery, divides into two branches and forms the carotid and cavernous plexuses. The chain is variable from individual to individual. Preganglionic fibers leave the spinal cord in the ventral root and run through the white rami. Postganglionic fibers pass by way of the gray rami to the peripheral nerves. These fibers are unmyelinated. Many fibers run from the chain to the vessels, viscera, etc. The most important of these are the splanchnics, the great splanchnic arising from the sixth to the tenth thoracic, the lesser splanchnic from the eleventh and twelfth, and sometimes the tenth ganglia. The fibers are distributed to the various abdominal plexuses. The splanchnic nerves, however, contain afferent fibers and also preganglionic fibers. The inferior cardiac nerve and filaments to the lungs, aorta and esophagus arise in the inferior cervical and first thoracic ganglia. Under the name sympathetic system are included the cells of the vertebral ganglia with their axons of motor or secretory function, spinal neurons of the sympathetic column whose axons end in the vertebral ganglia, and finally those cells of the central nervous system that convey impulses from the higher levels to the sympathetic column of the neuraxis. In the so-called sympathetic nerves there are also fibers belonging to the cerebrospinal system and parasympathetic fibers, so that the interpretation of phenomena observed to occur when these nerves are destroyed must be made with care. The sympathetic system sends numerous fibers to the skin, muscles, bones, vessels and viscera, and these fibers always are mixed with others of dissimilar origin, except in the gray rami. How much these sympathetic fibers enter into the functions of motion and sensation is still under discussion.

The report is divided into two parts. In the first the author takes up the various tests for sympathetic function and estimates their intrinsic value. In

the second part he discusses the localizing value of the results. Each section is preceded by a consideration of the physiology as determined experimentally. In the application of these observations to clinical neurology the cases that showed lesions of the sympathetic system alone are studied.

VASOMOTOR EFFECTS

Section of the sympathetic nerve in man is followed by:

1. *Hyperemia.*—This is most noticeable in the cheeks and ears. It also is seen in the conjunctiva, choroid and retina and in the nasal mucous membrane. Sometimes ephemeral, it may last for many months. It is usually more pronounced at the periphery. The palms, soles and nails particularly are affected. The skin is bright red rather than cyanosed. Cerebral hyperemia is observed, even years after cervical sympathectomy. A neurasthenic syndrome supposed to be due to this cerebral hyperemia has been described by Néri in sympathectomized subjects, but the same syndrome is found in many wounded men in whom trauma of the sympathetic has not occurred.

When the hyperemia is slight, it may be brought out by elevation of the limb, muscular effort, preliminary exclusion of blood by Esmarch's bandage, or some such test as the Pirquet. Elevation makes the healthy limb pale, and lowering causes congestion of the denervated limb. During muscular effort the face on the injured side becomes flushed. This vasodilatation is inconstant and often is transitory. If a considerable difference of temperature exists, the healthy limb may be cyanosed, thus appearing more congested than the other.

2. *Hyperthermia.*—The temperature of the sympathectomized limb is higher, particularly during the days following section. It may persist, however, after the color of the two sides has become equalized. If there is a difference of only a few tenths of a degree as registered by thermometers, the external conditions surrounding the two limbs must be controlled carefully. Thermal asymmetry is increased by chilling and may reach 8 or 10 degrees C., but exposure to extreme cold, such as dipping the hands in ice water, causes a sharper but more transitory fall in the denervated hand.

By moderate exercise the temperature of the denervated limb is raised above that of its fellow, but if the exercise is violent or prolonged the healthy limb becomes warmer, partly because of its more active motion. Carefully controlled tests sometimes must be made for one to be certain of this thermal asymmetry. Under generalized chilling, with the patient resting, the denervated limb cools off much more slowly. When the whole body is warmed, the temperature of the sympathectomized side rises much more quickly. An easier test is to have the patient dip his hands in ice water for five minutes and test the temperature at intervals after removal. The rise in temperature is much swifter on the paralyzed side. If the hands are dipped in hot water and later removed, the temperature on the healthy side falls more rapidly.

3. *Arterial Pressure.*—After sympathectomy, the pressure falls from about 3 to 3.5 mm. of mercury. There may be a period of heightened tension immediately following operation and a considerable fall, but equality is soon reestablished. The fall in pressure usually is bilateral. After exercise the oscillations obtained with the Pachon instrument are more pronounced on the healthy side. Warming is a useful test when there is doubt as to whether the sluggish circulation is the result of physiopathy or vascular changes. After heating, the oscillations in the diseased limb are more pronounced than on the healthy side, the opposite of the conditions found in arterial disease.

4. *Venous Pressure.*—This has not been studied carefully, although the veins of the paralyzed side are more prominent than those of the opposite side. In one case the venous pressure was 29 mm. on the side of the lesion, and 21 mm. on the healthy side. Gaertner's tonometer might yield interesting observations.

5. *Plethysmography.*—Hyperemia and hyperthermia do not always go together, a fact easily noted by placing one hand in cold and the other in hot water. A pale limb may be warm owing to rapid circulation. Plethysmography, used to measure the amplitude of the circulatory oscillations, may bring out important differences. The instrument is particularly valuable for testing the vasomotor reflexes. Changes in one limb often are accompanied by opposite changes in the other.

6. *Capillaroscopy.*— This yields important information in Raynaud's disease, but the relation of the sympathetic system to this disease has not been clarified. Its usefulness remains to be proved.

7. *Dermographism.*—The white streak formed by drawing a pointed instrument along the skin is exaggerated in areas of vasomotor paralysis. This excessive contractility of vessels is comparable to the idiomuscular excitability of paralyzed muscles, probably a local reaction. The red streak that follows the white one also is more marked and more prolonged on the diseased side. The "streak painful" arising in the neighborhood of a hard scratch is absent in the denervated area, although such a streak may be raised in the analgesic areas of syringomyelic persons. It is probably an axon reflex. The stimulus from the periphery runs centripetally, but in its course encounters a bifurcation that carries it toward the periphery by way of the blood vessels. This type of dermographism seems to follow sensory and vasodilator pathways rather than sympathetic fibers. Sometimes, after paralysis of the sympathetic chain, this red streak is observed more on the paralyzed than on the healthy side. The appearance of the preliminary white streak may be the result of temporary inhibition of the vasodilator fibers. Factitious urticaria may occur without any demonstrable lesion of the nervous system; its mechanism is as yet unexplained. The wheal stops at the desympathectomized area. Dermographism, however, has yielded few data of importance in the study of the sympathetic system.

8. *Pressure Pallor.*—The thumb of the observer is pressed on the back of the hand and removed. The time between removal and the return of normal color is measured. The time at 20 degrees C. is two seconds, less than one second at 40, and ten seconds at 2. Disappearance of the pallor is quicker on the sympathectomized side, but in cases of irritation it is prolonged. Before testing, the two limbs should be brought to the same temperature.

9. *Vasomotor Reflexes.*—The vasoconstrictor reflex is diminished or lost on the sympathectomized side, whereas the vasodilator reflex may be exaggerated. Chilling often is employed, but painful stimuli may be better. Pricking the affected palm sharply several times with a pin causes elevation of temperature on the same side and depression with sweating on the other. This shows what the physiologists have insisted on, that vasomotor reflexes are bilateral. A piece of ice placed on the neck or chest in the midline will bring about changes in the temperature, color and volume of each hand. Results are variable, however, in normal persons. The vasoconstrictor reflex is absent on the side deprived of sympathetic innervation. Hyperthermia and vasodilatation, however, may be the result of irritation of the vasodilator fibers rather than of constrictor paralysis.

The most useful of the vasodilator reflexes is the nasolacrimal. Irritation of the nasal mucosa is followed by congestion of the nose and conjunctiva, lacrimal secretion on one side and bilateral myosis. It should be tested on both sides. This may bring out latent anisocoria in pulmonary disease; it is lacking in some cases of tabes and is exaggerated in facial neuralgia. According to Miraillé and Weil, the reaction is lacking in peripheral facial paralysis but is unaffected in cases of lesions proximal to the geniculate ganglion. It is not a pure sympathetic reflex.

Vasodilatation in Response to Application of Mustard: Reddening of the skin is found in cases of section of the spinal cord and even of the peripheral nerves, provided the time for complete degeneration has not elapsed. This phenomenon is explained by Bruce on the ground that each peripheral fiber bifurcates, one branch going to the skin and the other to the vessels. The irritation transmitted by the peripheral branch is transferred directly without relay to the vascular branch. In other words, this is another example of the axon reflex. The reaction is lacking if the peripheral nerve is degenerated, but persists if the root is destroyed. In this there is a distinct diagnostic means between neuritis and radiculitis. The reaction is more pronounced in the sympathectomized area, so that it cannot be considered a test for the sympathetic system directly. If applied in a hyperesthetic area, mustard may cause marked blanching. When mustard fails, a high frequency current may bring about a marked vasodilatation.

10. *The Oculocardiac Reflex.*—This is inconstant, probably belonging to some system other than the sympathetic. The celiac reflex is too variable to be of use in determining organic conditions of the centrifugal or centripetal pathways.

SECRETIONS

Interruption of the sympathetic chain suppresses perspiration in corresponding areas. In section of the thoracic chain, the shirt is entirely dry in the axilla; the hand feels like parchment. Even during muscular exertion the affected parts remain completely dry, and the same is true in response to heating. Sudoral reflexes are obtained by sharp pinpricks on the affected hand. It remains dry, while the opposite hand becomes more moist. Sweating in the course of the Bárány examinations is not found on the side on which the sympathetic nerve is paralyzed. Likewise, the perspiration resulting from emotional disturbances is absent from sympathectomized areas. The exact limits of such areas can be determined by placing turmeric or dry silver nitrate paper on the skin.

Lacrimal secretion is increased during the first few days after cervical sympathectomy. It is the result, probably, of hyperemia. The fluid is less watery than the "trigeminal" secretion. Hypersecretion of the meibomian and ceruminous glands has been noted in cases of cervical sympathectomy. Salivary secretion is partly under the influence of the sympathetic system, the fluid being viscous and small in quantity. It has not been studied in cases of disease of the sympathetic system. Exaggeration of lacteal secretion has been found in syringomyelia and tabes, but the rôle of the sympathetic system is yet to be defined.

SMOOTH MUSCLES OF THE SKIN

The smooth muscles of the skin comprise the arrectores pilorum, the muscular fibers of the areola and nipple, the dartos of the penis and scrotum, the oblique fibers of the skin and those of the glands of the skin. In man, the arrectores are found on the neck, trunk and limbs, except for the hands and feet. They

are found in the scalp, the beard and the temples and in some people over the forehead. They are lacking in the eyelids, the cheeks, the nose and the nasolabial region. The pilomotor muscle responds to direct and reflex stimulation and to pharmacodynamic agents.

There is a normal and variable pilomotor tonus. The reaction to local stimulation does not disappear after section of the nerve, but there is a difference suggesting that the nervous system enters into play. The local reaction is brought out by stroking the skin. Gooseflesh appears locally after a considerable latent period, and disappears slowly.

The Pilomotor Reflex.—A reflex occurs when the reaction is observed at a distance from the point of excitation. The most common excitant is deep pinching of the border of the trapezius, and stroking or tickling of the subaxillary region. Faradization, or chilling the skin with a block of ice or ether sponge, also produces a reaction. The stimulus must be horripiligenous or must cause a disagreeable thrill or shiver. The reflex is strictly homolateral, thus differing from the vasomotor and sudoral reflexes, which are bilateral. The excitation must be forceful and sometimes prolonged. When the stimulus is repeated several times it loses its effect, but the reflex may be brought out again by a change in the stimulus. A weak reflex from the neck may not go below the umbilicus, or a weak one from the abdomen or sole of the foot may not reach above. Sometimes, however, cervical stimulation brings out the reflex on the lower extremity before the upper one. The clinician should attempt by reinforcement to secure a total reflex. The lighting must be arranged carefully in order to throw the utmost of cutaneous shadows from the gooseflesh. On bilateral symmetrical stimulation there is bilateral symmetrical response, an important matter.

The mammillo-areolar muscle contracts in response to local irritation. It also contracts in response to stimuli bringing out the pilomotor reflex, but is apparently independent. The smooth muscle of the dartos responds in an analogous manner to local excitation and to stimuli at a distance. The last, however, becomes bilateral, except in the female and in those with cleft scrotum. The contraction is obtained in 90 per cent of persons by scratching the sole of the foot, and by pinching the nipple. In old persons, whose skin is atrophic and in whom the pilomotor reflex no longer is striking, a slow sliding movement of the skin may be seen on stimulation, probably caused by the presence of smooth muscle sheets in the skin. This is variable, however, and seldom is seen.

Trophic Disorders.—The sympathetic nerve has been blamed for many trophic disorders, and operations on it have been performed on their account. In healthy animals sympathectomy does not cause trophic disturbance, but cutaneous lesions appear in sickly persons. The great number of operations performed on the sympathetic nerve for exophthalmic goiter, epilepsy, angina pectoris, Raynaud's disease, etc., have left no trophic disturbances, so that the sympathetic nerve cannot be blamed for them under other conditions. The only differences observed in the denervated skin are slight branny desquamation, palmar keratosis during the period of sweat suppression, and the appearance of sudamina during regeneration. Irritation of the sympathetic nerve may bring about greater trophic changes than its paralysis. The favorable results obtained by sympathectomy probably are caused in a large measure by the resulting hyperemia with better nutrition of the skin. Another factor is the enforced rest of the limb following operation. The sympathetic nerve probably is not responsible for the hypertrichosis or alopecia sometimes observed following nerve wounds.

Edema.—This has been observed in denervated areas, but it is slight and inconstant.

Pigmentation of the Skin.—This may be a sign of disease of the sympathetic nerve, but it is far from being proved. Sometimes scratches become pigmented. The skin of the sympathectomized area is sometimes pigmented, but there are usually other causes demonstrable.

LOCALIZING VALUE OF SYMPTOMATOLOGY

Although the human sympathetic system is not as open to experiment as is that of animals, a series of observations will show that the observations made on animals are quite applicable to man. In cases of transection of the cord at different levels, giving definite level symptoms, the extent of the pilomotor reflex will indicate the limit of extension of the uninjured fibers. Moreover, when the cord is sectioned a new spinal reflex appears, comparable to the reflex of spinal automatism. This reflex covers the territory innervated by the spinal segments below the lesion. A study of the two reflexes in each case, together with determination of the level of section, brings out the extent of the fibers of the upper and lower uninjured segments.

From more than forty personal observations, Thomas finds the following: The superior cervical ganglion, whose fibers innervate the head and neck, receives preganglionic fibers from the first four and possibly the fifth thoracic segments. The inferior cervical ganglion, innervating the upper limb, receives preganglionic fibers from the fourth, fifth, sixth and seventh thoracic segments, possibly overlapping slightly with the third and the eighth. The lumbosacral ganglia that innervate the lower extremity receive their fibers from the tenth thoracic to the second lumbar segments. Each thoracic ganglion from the sixth to the twelfth receives fibers from two or three spinal segments lying above and below its level. These data hold true for the pilomotor reflex. The spinal center for the mammillo-areolar reflex is located approximately from the fourth to the eighth thoracic segments of the cord. The center for the dartoic reflex lies below the tenth thoracic segment.

Sudorific centers in man occupy, in the main, the same locations, and can be delimited by appropriate methods, because sweating in response to irritation above the level of the lesion stops at a fairly definite level, whereas the spinal sweating reflex will not reach above a certain level. Vasoconstrictor centers seem to occupy the same levels as the pilomotor and sudorific centers in the spinal cord. An interesting phenomenon is the fall in temperature that takes place during the exhibition of the reflexes of defense. A level of thermal difference sometimes may be perceived by the hand.

SYNDROME OF THE SYMPATHETIC PATHWAYS

Cervical Sympathetic Trunk.—Section of this cord is followed by the oculo-pupillary syndrome of Claude Bernard-Horner. It consists of narrowing of the palpebral fissure, enophthalmos, myosis and lowering of the intra-ocular tension. A change in the color of the iris is sometimes noted. The interpretation of these ocular signs is still debated. Absence of the pilomotor reflex over the head and neck is found in sympathetic paralysis. Langley has shown experimentally that these fibers do not follow the vessels. The pilomotor and sudorific fibers arise in the superior cervical ganglion and run out by the first four cervical nerves and the trigeminal. The last branch follows the carotid division to anastomose with the gasserian ganglion. The distribution of the

areflexia is always radicular. A lesion of the carotid division may cause a pure trigeminal and oculopupillary syndrome.

The Thoracic Trunk.—If the sympathetic nerve is interrupted at the third thoracic root, the oculopupillary syndrome is lacking; there is only diminution of the other reflexes over the head and neck. There is complete sympathetic paralysis of the upper extremity, including the second and third thoracic root areas.

The stellate ganglion is formed by the fusion of the inferior cervical with the first and sometimes with other thoracic ganglia. If it is destroyed with the trunk there is sympathetic paralysis of the head, neck and upper limb. Nevertheless, the second and third thoracic nerves retain their relations with the sympathetic, and the pilomotor reflex is observed on the inner side of the arm. There is thus considerable overlap. In cases of sympathetic irritation, such as occurs not infrequently in Potts' disease, there may be sweating of one quadrant of the body, with ocular protrusion, slight pupillary dilatation and exaggerated pilomotor reflex. Sympathetic syndromes are changeable, for the fibers regenerate.

Interruption of the thoracic trunk below the fifth or sixth segments diminishes the reflectivity in the corresponding areas, and when the ganglia themselves or their rami are destroyed, sympathetic reflexes are lacking in the corresponding radicular territories. As a rule, simple interruption of the sympathetic trunk in the thoracic region is not followed by any disturbance, because each ganglion receives fibers from several nerve roots above and below, and because at this level the section would not interfere with the preganglionic fibers for the limbs.

Lesions Below the Tenth Thoracic Segment.—Sections in this region reduce the reflectivity over the abdomen and lower extremity progressively as the section is made lower. Every interruption of the trunk below the second lumbar segment is followed by complete loss of sympathetic reflexes below the cutaneous area of this root, but in the area of the root the reflexes are sometimes more marked. If the trunk is divided lower down, the disturbed reflectivity recedes in segmental fashion.

Syndrome of the Rami Communicantes.—In a case of tuberculous spondylitis, with destruction of the disk between the eighth and ninth thoracic vertebrae, the pilomotor reflex was absent in the eighth and ninth root territories. The disease of the rami was checked by careful dissection post mortem. This shows that the syndrome of the rami is altogether radicular. Phenomena of ramal irritation sometimes are observed in restricted segmental areas. Thomas warns that before operations on the sympathetic system the patient should be examined carefully with regard to vasomotor, pilomotor and sudorific reflexes, in order to be certain that the phenomena observed after operation are in reality due to operation, as well as to make sure that the sympathetic system has indeed been operated on!

Lesions of the rami communicantes produce sympathetic phenomena unaccompanied by any symptoms referable to the cerebrospinal system, even in the finest degrees of epicritic sensibility.

Syndrome of the Sympathetic Fibers Outside the Trunk and Rami.—The sympathetic fibers arising in the vertebral ganglia run largely in the nerves. Others immediately join the periarterial plexuses. All along their course the arteries receive fibers from the accompanying nerves. Therefore the symptoms of sympathetic disease will differ according to the location. The symptoma-

tology of the peripheral sympathetic system should be divided into that of the peripheral nerves and that of the vessels:

Syndrome of the Arterial Sheath: The immediate effect of ligation of a large vessel is chilling of the peripheral parts, followed by a rise of several degrees after a few hours. The temperature rises only with the establishment of the collateral circulation giving these parts a larger blood supply, for the vasomotor fibers are interrupted. Similar effects are noted on resection of the arterial sheath. The circulatory disturbance resulting from this operation usually disappears in two weeks. The syndrome is exclusively vascular and thermic in character, no change taking place in the pilomotor or sudorific reflexes. The reduction in secretion of sweat sometimes observed is probably the result of the reduction in sympathetic irritation present before operation. The variability of the vasomotor effects and their lability probably depend on the receipt by the arteries of vasomotor fibers from the accompanying nerves throughout their course. The sympathetic system exercises a greater effect on the cutaneous circulation through the nerves than through the vessels.

Operations on the arterial sheath may also involve fibers other than sympathetic ones, sensory and vasodilator fibers. Some of the results point strongly to disturbance in the sensibility of the arteries operated on.

Sympathetic Syndrome of Diseases of the Peripheral Nerves: Simple immobilization of a limb will cause it to cool. Even if the sympathetic fibers are not directly involved, there will be disturbances in the vascular reactions of the paralyzed limb. The explanation is debatable and has little place in this report on organic conditions.

In traumatic lesions of the peripheral nerves, the sympathetic phenomena differ according to whether the lesion is located above or below the coalescence of the ramus with the nerve trunk. The cervical roots and the lower three lumbar and the sacral roots do not contain preganglionic sympathetic fibers. Therefore, lesions proximal to the rami will not cause any disturbance of the sympathetic system. The absence of pilomotor and sudorific reflexes in the anesthetic area in lesion of the brachial plexus demonstrates that the lesion lies below the coalescence of the rami. Similar sensorimotor disturbances without sympathetic disturbance locate the lesion within the spinal canal. The rule is less valuable when the thoracic segments are affected, because all the ventral roots contain preganglionic fibers. Interruption of the fifth, sixth, seventh and eighth ventral thoracic roots renders the upper extremity unresponsive to sympathetic stimulation. The lower limb loses its sympathetic reflexes when the tenth, eleventh and twelfth ventral thoracic roots and the first and second lumbar roots are interrupted. Interruption of the first thoracic root causes the oculopupillary syndrome without interfering with the pilomotor and sudorific reflexes.

In cases of paralysis due to lesions below the coalescence of the ramus with the peripheral nerve, the pilomotor fibers run with the sensory fibers to their radicular distribution. Pilomotor and sudorific fibers may not be included in the same bundle. The same general rule holds for the trigeminal nerve. Section of the root does not cause any sympathetic disturbance, but division of the branches induces sympathetic paralysis in the corresponding areas.

In more peripheral paralyses the pilomotor reflex disappears from areas closely corresponding to the anesthetic areas, but the local pilomotor response may be exaggerated.

The temperature range is different according to the seat of the lesion. When a nerve is sectioned, the area is warmer at first, but is cooler than the healthy

areas after a few days. When a main trunk is affected, however, the temperature falls and remains low until the fibers have regenerated. In either case not only the sympathetic but also the vasodilator fibers are affected. For instance the application of mustard in a completely denervated area will not cause a cutaneous reaction, whereas if the sympathetic nerve alone is involved, the reaction persists or may be exaggerated. At any rate, section of a nerve trunk does not deprive the limb of vasomotor control as long as the main vessel is intact. The hyperthermia observed soon after section of a nerve trunk may be due to the fact that the vasodilator fibers lose their excitability more slowly than the vasoconstrictor ones. The median and ulnar nerves, although they have rich vasomotor and secretory representation, contain few pilomotor fibers. The plantar nerves of the lower extremity are similar.

Destructive lesions of the dorsal roots do not disturb the pilomotor and sudorific reflexes; although if it is true that the dorsal roots contain vasodilator fibers, the vasomotor reactions may be interfered with.

Irritative lesions of the roots beyond the coalescence provoke manifestations in the same distribution but opposite in character to destructive lesions; that is, hyperhidrosis and exaggeration of the pilomotor response. These signs usually are accompanied by pain, hypertonia and contracture of voluntary muscles. Vasomotor responses may be of either sign. Vasodilatation and hyperthermia, as permanent manifestations, are more frequent in irritative lesions than in paralytic ones. Causalgia is accompanied by signs of both paralysis and irritation of the sympathetic system. Irritation of the dorsal spinal roots, as in tabes, sometimes is associated with lively sympathetic reflexes.

During regeneration of sectioned nerves the reappearance of the pilomotor reflex is rather precocious, coming by isolated points or blotches. The pilomotor reflex returns usually with tactile sensibility. Apparently there is never any erratic distribution of the pilomotor fibers during regeneration. Muscular effort seems never to be associated with pilomotor response. Lacrimation sometimes is observed after operations on the parotid when the masticator muscles are used.

Nontraumatic Conditions.—In meralgia paresthetica, the pilomotor reflex is absent in the anesthetic area. In herpes zoster, the rôle of the sympathetic nerve is only accessory and is observed in a minority of cases. The pilomotor reflex is absent over a fairly large area and may be exaggerated in contiguous areas. In peripheral neuritis it is usual to see the sympathetic system less affected, or involved later than the cerebrospinal.

SYMPATHETIC DISORDERS IN LESIONS OF THE CENTRAL NERVOUS SYSTEM

Complete section of the spinal cord brings about a series of phenomena, some of which are caused by suppression of continuity of the nervous axis and others by liberation of the parts below. The temperature rises below the level of section, particularly in the distal portions, but becomes variable when the reflexes of spinal automatism develop. The response to chilling is less in the parts below the lesion. The vasoconstrictor reflex elicited by chilling the chest with ice does not take place below the lesion. The vasomotor reflex likewise is lacking at lower levels. The pilomotor reflex elicited by irritation of the trapezius stops in the parts innervated by the lowest uninjured segment. The pilomotor reflex thus usually extends beyond the line of anesthesia, only coinciding with it when the sympathetic trunk or its rami are interrupted two or three segments above. The same rule holds for the sudorific responses.

Moreover, Horsley showed that, if the patient was subjected to an elevated temperature, sweating first took place in the cutaneous areas innervated by the segment just above the lesion. This may be of localizing value. Reflex dermographism usually is more pronounced below than above the lesion. Rarely is the line interrupted, and then probably only because of coincident involvement of the rami. Another sign of possible localizing value is the fact that in drawing the point of a pin from the anesthetic to the sensitive area, when the line of demarcation is passed the cephalic pilomotor reflex is provoked.

A variable period after section of the spinal cord, the portions below the lesion take on their own activity. At this time the temperature of the affected limbs falls, and a series of spinal sympathetic reflexes hitherto concealed comes into play. These are analogous to the reflexes of spinal automatism. They usually do not extend above the line of demarcation.

A whole series of reflexes, vasomotor, sudorific and pilomotor, may be elicited by proper stimulation of the parts below the transverse lesion, whereas excitation in the sensitive regions produces no change in the same areas. Thermal instability is particularly noticeable in the toes. Similar variations may be noted in the course of plethysmography. The warmer limb is often found slightly more infiltrated by edema.

The spinal pilomotor reflex appears about the same time as the reflexes of defense. It may be elicited by pricking, scratching, pinching, heat, cold, etc. Passive movement of the limbs is peculiarly effective. It is homolateral with the stimulation, but occasionally becomes bilateral when unilateral stimulation provokes crossed reflexes. Gooseflesh sometimes appears apparently spontaneously, although some visceral movements are probably the exciting stimuli. The same is true of sweating. The spinal pilomotor reflex may advance above the line of anesthesia. The spinal sudorific reflex is more capricious than the pilomotor reflex, but usually runs pari passu. Warmth is the best stimulus for cephalic sweating, although acetylsalicylic acid or pilocarpine may be used; the spinal automatic reflexes most frequently bring out the spinal sudorific reflexes.

Complete section of the cervical cord produces the oculopupillary syndrome with total absence of cephalic sympathetic reflexes. The spinal vasomotor, sudorific and pilomotor reflexes extend up to the level of anesthesia.

A lesion at the level of the second and third thoracic segments leaves the eye normal and a slight pilomotor response over the head and neck. The spinal reflex extends all over the skin including the face, neck and head, but is more intense in the upper extremity. If the lesion involves several segments the spinal reflex does not extend up so far.

As the level of the lesion extends lower, there is a step-like progression of the cephalic pilomotor reflex accompanied by step-like regression of the spinal reflex. When the two overlap there is only a small area of complete destruction, but when the areas of the cephalic and spinal reflexes are separated, the phenomenon indicates destruction of several segments of the cord. When the upper limit is below the tenth thoracic segment, the cephalic reflex covers the lower extremities, showing that this segment innervates the lower extremities. In lesions below the tenth thoracic segment and above the third lumbar segment, the spinal reflex still can be obtained. Below the last level, sympathetic phenomena are not observed from section of the spinal cord.

In cases of hemisection of the cord, the temperature rises on the paralyzed side, arterial pressure rises and perspiration and the cephalic pilomotor reflex disappear. Later, the skin becomes cyanosed and the cephalic sudorific and pilomotor responses again become evident. The spinal pilomotor reflex is

difficult to obtain. The sympathetic syndrome occurs only when the hemisection involves the lateral basic column of the cord.

Nontraumatic Conditions of the Spinal Cord.—Transverse myelitis, from the sympathetic point of view, most closely resembles traumatic section of the cord. The spinal pilomotor reflex is obtained much less frequently, however, than in complete transverse lesion. However, it is occasionally possible by the test to ascertain the upper and lower limits of the lesion. The test may give some indication of the nature of the lesion, for if the cephalic reflex is present throughout the body it means that the sympathetic fibers, which lie close to the lateral horn of the cord, are preserved and that the lesion does not extend to that depth. In syphilitic meningomyelitis the pilomotor reflex is entirely normal, although the line of anesthesia may reach above the tenth thoracic segment.

Potts' Disease.—There is often a discordance between the characteristics of the cerebrospinal system and the sympathetic system in this disease which most often can be referred to involvement of the radicular fibers and the sympathetic chain. The filaments often are caught in a caseous mass, and localized signs sometimes are produced. At other times they may be stretched over abscess walls. When the spondylitis heals, the abnormal sympathetic symptoms disappear. "When syndromes of the sympathetic trunk or of the rami communicantes are associated with spastic paraplegia, the diagnosis is turned toward spinal compression by vertebral disease. Potts' disease is the most frequent cause."

In multiple sclerosis with paraplegia, lack of a pilomotor reflex in some area not connected with the lesion is an indication of multiple foci. These losses of reflex activity often are transient.

In all cases of chronic poliomyelitis or of amyotrophic lateral sclerosis, the pilomotor reflex is intact. In the acute cases, involvement of the lateral horn may bring about temporary abolition of the reflex.

When the lateral horn of the spinal cord is injured, as in syringomyelia and kindred conditions, sympathetic phenomena may be present early. The oculopupillary syndrome is present in 15 per cent of syringomyelic persons, according to Schlesinger. Vasomotor, sudorific and trophic disturbances in the disease are well known, and may be either of the irritative or paralytic variety. Among the former are hyperhidrosis, sometimes limited to one side of the body or even to one segment, and spontaneous pilomotor phenomena limited to localized areas. Pilomotor tonus is increased and the reflex activity exaggerated. In other cases the reflex activity is disturbed or abolished. It is absent in the areas of sensory dissociation. Occasionally, a crossed spinal reflex is obtained. Sudorific and vasomotor reflexes likewise are often lacking. Dermographism often is pronounced. The marbled aspect of the skin, with cyanosis, indicates sympathetic excitation.

Edema frequently arises after injuries to the spinal cord, but is probably not caused by the sympathetic nerve, for it occurs in lesions of the conus, and in many cases no sympathetic disturbance can be made out. Pigmentation, also, though occasionally seen in disease of the spinal cord, probably is the result of some cause other than the sympathetic.

Diseases of the Brain-Stem.—The oculopupillary phenomenon is found on the same side as the lesion. The temperature is likewise elevated; anhidrosis is observed occasionally, but more often such irritative phenomena as unilateral sweating, chilling and pallor occur. Unilateral absence of the pilomotor reflex may be caused by the accompanying hemianesthesia, and should not always

be interpreted as the result of sympathetic involvement. The sympathetic fibers seem to lie in the lateral reticular formation.

Conditions of the Cerebrum.—In the thalamic syndrome the extremities opposite the lesion often are red and warm, but may be cyanosed and cold. Hemihyperhidrosis and sometimes exophthalmos, mydriasis and seborrhea have been observed. The effect of warming is usually more marked on the paralyzed side. In cases of hemiplegia, vasomotor asymmetry frequently is found, and the affected limbs may be hyperthermic at first, but usually the temperature falls below the healthy side. Responses to the application of ice in the midline are inconstant, but the paralyzed limb is usually more labile than the other. In paralysis agitans and in encephalitis, hypersecretion often is observed, but needs further study. Epilepsy affects not only striated but also unstriated musculature giving such symptoms as chilled and sweating hands. A unilateral sympathetic syndrome has been found clearly in migraine. A crisis of pallor, chilling, gooseflesh and sweating sometimes may be looked on as an epileptic equivalent. The pilomotor reflex cannot be obtained during the fit.

PHARMACODYNAMIC TESTS

Pharmacodynamic tests sometimes are useful in bringing out differences on the two sides of the body, but should be interpreted with care. Amyl nitrite, although not acting directly on the sympathetic system, will cause a greater rise in the temperature of the ear on the sympathectomized side than on the other. Pilocarpine acts on the pilomotor and vasomotor nerve endings as well as on the secretory; it is useful in aiding the appearance of the pilomotor reflex. The local reaction produced by the subcutaneous injection of epinephrine is not of any diagnostic value as far as the sympathetic system is concerned.

Two properties of the sympathetic system remain to be considered, overflow (répercussivité) and selection. When a nerve is paralyzed by an organic lesion, the pilomotor reflex is absent in the corresponding area, but is exaggerated in the surrounding areas. In herpes zoster of the chest, the pilomotor and other sympathetic phenomena may be exaggerated in the upper extremity. In regard to selection, sympathetic phenomena can be brought about by a variety of causes, external and internal, but there seem to be shades of feeling that cause chilling and pallor to become manifest without sweating, or vice versa, and the same with gooseflesh. Although the sympathetic system is more or less a unit, under certain conditions the various anatomic parts enjoy a certain autonomy, probably resulting from their particular reaction pattern in the face of a central stimulus.

VISCERAL SYMPATHETIC SYSTEM

The sympathetic system inhibits smooth muscle tone of the alimentary tract, but constricts the vessels. There may be disturbance of the pulse rate in syringomyelia. A rise in temperature has been noted in serious injuries to the spinal cord. In the early stages, however, extremely low rectal temperatures may be noted. The rise in temperature, with acceleration of the pulse and fall in blood pressure, often is noted after operations on the brain. The sympathetic disturbances evoked by visceral crises probably are the result of pain. Meteorism often is present in diseases of the spinal cord. Vasodilatation by sympathetic paralysis may explain intestinal hemorrhages and the hematurias that sometimes follow spinal injuries. Finally, it may be well to recall that the glycosuria following puncture of the fourth ventricle is not present when the hepatic sympathetic fibers or the splanchnic nerves are cut.

THE SYMPATHETIC SYSTEM AND SENSIBILITY

The increased sensibility observed in limbs deprived of sympathetic innervation would tend to show that the sympathetic system exerts an inhibitory action on the fibers of sensibility. However, the effect probably is only the result of the richer blood supply and the increased warmth of the parts. Operations on the sympathetic system are painful, and various diseases that involve the sympathetic system, particularly causalgia, are horribly painful. These syndromes usually are caused by irritative lesions. Direct irritation of the sympathetic ganglia in man produces severe pain, as proved at various operations. This obtains whether the ganglia, the trunk or the rami are stimulated. It would therefore seem that the sympathetic system was partly sensory. On the other hand, sensory fibers have not been demonstrated. Transection of the cord below the tenth thoracic segment, for instance, does not prevent the cephalic pilomotor reflex from covering the limbs, but sensibility is abolished completely. Direct excitation of the sympathetic system probably produces its results through stimulation of some preganglionic fibers that accompany the nerves, fibers whose ganglion cells are situated in the spinal ganglia. These are the fibers that probably endow the sympathetic system with a peculiar form of sensibility like the protopathic form of Head. They probably give the arterial sheath its sensibility. In other words these fibers have borrowed sympathetic pathways to find their terminations. The reduction or abolition of pain caused by periarterial sympathectomy appears to be more the result of interruption of these trespassing fibers than of interruption of the sympathetic fibers themselves. The variability of the results and the frequency of painful areas in otherwise anesthetic patches lends force to such an argument. On the whole, the evidence is against the existence of a sensory sympathetic system; rather, the sensory fibers have borrowed the sympathetic pathway to the periphery.

THE SYMPATHETIC SYSTEM AND STRIATED MUSCLE

When the nervous system is intact, section of the sympathetic nerve produces only infinitesimal changes or none at all in muscle tonus. In injuries of the central nervous system section of the sympathetic nerve does not result in change in the tonus, according to Pollock, but to decrease according to other authors. The contractures of pyramidal and of extrapyramidal disease have not been favorably influenced by resection of the sympathetic. The rigidity has been reduced in certain cases in which it was due to peripheral nerve disease, but this is a complex matter.

SUMMARY

"The methods of examination of the sympathetic system passed in review are of two orders. One needs a complicated set of apparatus, and the procedure may be likened to physiologic experimentation, such as plethysmography, thermometry and capillaroscopy. The others are simple and scarcely surpass the limits of clinical observation. They suffice in the great majority of cases.

"How should one proceed, limiting oneself to the latter category?

"The examination of the patient should begin with a rapid inspection of the color of the skin, its temperature, dryness or moisture, and the presence or absence of gooseflesh. Asymmetry is quickly brought out, an important indication. It should first be determined whether such asymmetries are caused by local conditions preceding examination, such as clothing and heating. Repeated trials during the period of examination will reveal the differences caused by the surrounding temperature, peripheral stimulation, the impressionability of the subject, etc.

"The examination of the vasomotor apparatus is greatly facilitated if the patient has been in bed a long time, for example in the early morning, the four limbs having been exposed to the same temperature for several hours. The body is then uncovered and immobility is commanded, especially if there is unilateral paralysis. Under these conditions the appearance of anisothermy between two homologous parts, an excessive difference between the upper and lower limbs, becomes an important observation. Asymmetry in the face usually is evident if the room temperature is not too high.

"A high value should be set on the cooling test. The absence of chilling in a limb that is not paralyzed or contractured and that shows no disturbance of the nervous or vascular systems, naturally orients the diagnosis toward the sympathetic system. The examination of thermic control is completed by the study of modifications induced by alternate exercise and repose.

"When the foregoing conditions are not fulfilled, the test of anisothermy is open to confusion. When variations are found it may be questioned whether there is too great chilling on one side or not enough on the other. Chilling does not have the same significance if it occurs in a paralyzed limb as if it occurs in one whose power is intact and activity is normal. The absence of cooling, on the other hand, may be interpreted equally well either as excitation of the vasodilator system or as paralysis of the vasoconstrictor system. Doubt is abolished if the sudorific and pilomotor mechanisms respond in the same manner, but in diseases of the central nervous system these three functions do not always suffer simultaneously or equally. The vasomotor apparatus alone is affected in lesions of the arterial sheath. When sympathetic fibers are involved along with others as in peripheral nerve lesions, the temperature falls instead of rises. The questions raised by the study of vasomotor disturbances are numerous and complex.

"The absence of moisture or sweating on half the face or on one limb has the greatest significance when both limbs are exposed to the same physical and physiologic conditions.

"In a large number of subjects, nevertheless, the skin remains dry unless subjected to considerable active or passive warming. The last is the only test that can be used with paralytic patients, and it needs time and a special apparatus. To induce sweating the physician has at his disposal pain as a stimulus, but the sweating appears usually only on the palms of the hands; the procedure is not infallible; the information obtained is incomplete and is adequate in only a small number of cases. Inequality in the secretion of homologous parts is of doubtful significance, for it may mean suppression on one side or exaggeration on the other. Only by comparing this sweating with that of the rest of the body and its variations and by multiplying the tests can an opinion be gained.

"The examination of the vasomotor and sudorific systems is thus long, difficult, and of questionable interpretation in a sufficiently large number of cases.

"On the contrary, the pilomotor reflex is a test that gives rapid and precise results on the degree of reflectivity of the sympathetic system. According to the distribution of the areflexia or hyperreflexia, the superposition, or lack of it, of one or the other over areas of anesthesia or hyperesthesia gives indications of great importance as to the location and extent of the lesion. Of course the intensity of the reaction is not the same in all people or in the same person always — sympathetic reactions are particularly individual and variable; some fat, greasy skins are not strongly endowed in this regard. The cervical territory of the sympathetic does not respond with the same vivacity as do other regions of the body. But by varying the excitations, and by using pilocarpine, which is an excellent stimulus, in tests in rebellious subjects, almost always some interesting results are obtained.

"The pilomotor reflex is indubitably the most practical and rapid method of examination of the cutaneous sympathetic system. It is quicker than sudorific tests and is less subject to discussion than vasomotor reflexes or reactions whose interpretation is complicated by the physiologic antagonism of the vasoconstrictors with the vasodilators."

FREEMAN, Washington, D. C.

STRUCTURE, MOVEMENT, LOCOMOTION AND STIMULATION IN AMEBA. S. O. MAST, J. Morphol. **41**:347 (March 5) 1926.

Amoeba proteus contains a central elongated fluid portion (plasmasol), a rigid layer surrounding this (plasmagel), a thin elastic surface layer (plasmalemma) and a hyaline layer between the plasmagel and the plasmalemma which is fluid at the tip of active pseudopods and in certain other regions. The plasmasol is an emulsion. It consists of a fluid in which various vacuoles and granules are suspended. The plasmagel is probably alveolar in structure. It contains the same kinds of substances as the plasmasol, but some of the fluid appears to be gelated so as to form alveoli. The plasmalemma probably consists of interwoven protein fibers and a lipoid which fills the interstices.

The plasmasol is probably hypertonic; the plasmagel and the plasmalemma are probably semipermeable. These and other factors result in an excess of the inflow of water, stretching the plasmagel and the plasmalemma. When a pseudopod is formed, the inner portion of the plasmagel liquefies locally. This produces a local decrease in elastic strength resulting in the formation of a protuberance, a pseudopod. As this is formed, there is contraction at the posterior end, resulting in forward flow of the plasmasol and extension of the pseudopod. If the pseudopod is attached, the plasmalemma, being attached to the substratum and to the adjoining plasmagel, slides over the plasmagel above and remains stationary below, and rolling movement results. If it is free, the plasmalemma is stretched out with movement in it equal on all sides. If the free pseudopods become attached to the substratum at the tip after they are thus formed, walking movement results. During locomotion of either type, the plasmasol continuously gelates at the tip of the extending pseudopods forming plasmagel, and the plasmagel continuously solates at the posterior end forming plasmasol.

Response is due largely to changes in the elastic strength of the plasmagel in the adhesiveness of the plasmalemma and in turgidity.

Locomotion in *Amoeba verrucosa* is in principle the same as in *Amoeba proteus.*

WYMAN, Boston.

MULTIPLE NEUROFIBROMAS ASSOCIATED WITH A TRUE ANGIONEUROFIBROMA OF THE ACOUSTIC NERVE WITH JACKSONIAN EPILEPSY AND OSTEOPOROSIS. G. W. T. H. FLEMING and H. A. COOKSON, J. Neurol. & Psychopath. **6**:104 (Aug.) 1925.

The authors report an interesting case in a man, aged 66, whose family history was negative except that a sister died at 57 with diabetes and a daughter, aged 27, had suffered with epilepsy since her seventeenth year. The patient was unable to write and probably unable to read. He began to suffer with epilepsy at 40, the convulsions being confined to the left side and only occasionally becoming generalized. During the last few years, he had become irritable and quarrelsome. When he was admitted to the hospital, the records showed that there were multiple tumors on both arms extending from the wrist to the shoulder, situated along the course of the principle nerve trunks. Otherwise, the physical examination gave negative results. The nervous and mental

examinations were unsatisfactory, owing to the patient's condition. Vision was obviously impaired. The patient apparently was deaf on the right side. He died after being in the hospial for about four months. At necropsy, it was noted that the bones of the cranial vault were soft. The dura was adherent to the calvarium and beneath it was a well marked pachymeningitis hemorrhagica interna. In addition to this, there was an endotheliomatous thickening, about 10 by 10 cm., lying along the right sylvian fissure and the foot of the rolandic fissure. There was a little distortion, probably the result of pressure over the precentral area of Campbell. The right acoustic nerve showed a tumor which caused some pressure on the pons. In addition to this, all the large nerve trunks in both arms showed the presence of fusiform swellings of various sizes along their course. On histologic examination, the tumor of the eighth nerve proved to be an angiomatous neurofibroma and the tumors of the peripheral nerves showed the characteristic picture of fibroneuroma. The growth from the dura mater was an endothelioma. The portion of a rib showed the histologic picture of osteoporosis.

POTTER, Akron, Ohio.

A CONTRIBUTION TO THE CAUSES OF HALLUCINATIONS OF THE VISION OF MOVEMENT. T. M. SACRISTAN, Arch. de Neurobiol. **4**:208, 1924.

Sacristan describes an interesting case of hallucinations of the vision of movement in a woman, aged 30, who had had smallpox at the age of 10, and later in life contracted syphilis. At the time of the neurologic examination, there was a strongly positive Wassermann reaction in the blood, while the cerebrospinal fluid was normal. The pupils and ocular fundi were normal. The patient declared that her illness began after the death of her mother, and was later increased by a love affair. At first she began to suffer from somatic hallucinations, which she thought were due to a drug put in her food by a woman who was jealous of her. These hallucinations, described as something creeping from her body to the throat, and as terrible beasts running over the chest, ceased after a few days. Then she began to have hallucinations of a different type; she could see people falling from windows and the tops of the houses, and limbs of people falling off without bleeding. These hallucinations occurred with the eyes open or closed and caused terrible suffering; none took place when the persons concerned were present. She believed at the time that they were real, but when she found that the person concerned was sound in body and limb she corrected herself, saying that what she saw during the hallucinations were visions sent by an enemy, the "bad spirit," to cause her suffering.

The author reviews and discusses the few cases of this kind in the literature, and concludes that his case belongs to the group of elementary hallucinations of the vision of movement in a patient suffering from paranoid schizophrenia. His opinion is based chiefly on the absence of disturbances of the vestibular apparatus as well as the absence of dizziness during the hallucinations.

NONIDEZ, New York.

THE IMPORTANCE OF ARTERIAL LESIONS IN THE PATHOGENESIS OF RAYNAUD'S DISEASE. HENRI GRENET and ISAAC-GEORGES, Ann. de méd. **20**:27 (July) 1926.

Most authors writing on this subject adhere to the theory advanced by Raynaud in 1862. He thought that the nutritive lesions in the environment of the arterioles of the skin were caused by spastic contractions of these vessels

due to disturbances of sympathetic innervation. He did not admit anatomic changes as etiologic factors.

Six of the patients in the eleven cases reported (ten women and one man) were syphilitic. Among the ten women, five were over 30, three had an early menopause, two had dysmenorrhea and two had hyperthyroidism. Under the capillary microscope, spasm of the capillaries of the skin was found in all cases. Examinations with the oscillometer showed that this spasm was present also in the arteries of the arm. This phenomenon was symmetrically bilateral in only five cases; in six cases it was confined to one arm. The histologic examination of small pieces of skin, which were removed from the area outside the diseased skin, revealed a striking change in the small arteries. The lumen was narrow, and there was proliferation of the endothelial layer with infiltration of the media.

From their clinical and histologic observations, the authors draw the conclusion that in Raynaud's disease the sympathetic disturbances of innervation (also manifest in endocrine disturbances) must be combined with anatomic lesions of the vessels (originating from syphilis or acute infectious disease). According to the varying prevalence of one of the two factors, one will find the manifold clinical pictures with preponderance either of the gangrene or of the spastic vasoconstriction.

WEIL, New York.

A CASE OF SACROCOCCYGEAL CHORDOMA. A. RICHARDSON and A. L. TAYLOR, Brit. M. J. **1**:862 (May 22) 1926.

The authors review briefly the pathologic and clinical aspects of fifty-seven previously reported cases of chordoma and report a new case in a man, aged 43, whose first symptoms began in November, 1924, with a small swelling in the lower part of the sacrum. The pain and swellings gradually increased, and in November, 1925, he was admitted to the hospital. On examination, there was found a slightly lobulated, rounded tumor, the size of a small tangerine orange, in the midline at the level of the junction of the coccyx and sacrum. It was attached firmly to the bone and slightly to the overlying skin. On rectal examination, the mass could be palpated in the hollow of the sacrum. At operation, the tumor was found to be firmly attached by a wide base to the lowest piece of the sacrum. The bone was eroded and infiltrated with the growth. The portion of the tumor removed was 2½ inches (6 cm.) in diameter, well encapsulated on its superficial surface and distinctly lobulated. On section, it was found to have an alveolar appearance, the lobules being separated from each other by thin, fibrous trabeculae. The nodules consisted of a whitish, gelatinous material. There were numerous small areas of hemorrhage throughout the tumor. Histologically, the tumor was made up of solid masses of epithelial cells with small round or irregular nuclei having a poorly defined chromatic network. The cytoplasm was granular. Mitotic figures were not found, and only a few cells could be classified as embryonic. There was a large amount of mucin throughout the structure.

A short bibliography is given at the conclusion of the article.

POTTER, Akron, Ohio.

THE EFFECT OF REDUCTION OF SKIN AND OF MUSCLE ON THE DEVELOPMENT OF THE SPINAL GANGLIA. S. R. DETWILER, J. Exper. Zool. **45**:399 (July 5) 1926.

In limb extirpations, both skin and muscle are reduced, and when a limb is grafted both these tissues are increased. In order to obtain a relation

between cell loss in developing spinal ganglia and either skin or muscle loss, two embryos were grafted together laterally shortly after the fusion of the medullary folds. This produced a considerable skin loss without a corresponding muscle loss. In such preparations, the spinal ganglia of the nerves supplying the fused sides of the components undergo a striking hypoplastic development. An average cellular reduction of 67 per cent is found in the ganglia of the brachial nerves, which have been rendered limbless. The ganglia of the sixth, seventh and eighth nerves undergo a reduction of 34 per cent. The data obtained from a quantitative study of skin loss, muscle loss and cellular losses, owing to fusion, were brought together into three pairs of simultaneous equations for consistent values of the coefficients. These values indicate that approximately 60 per cent of the cellular reduction in the spinal ganglia is due to skin loss and 40 per cent to muscle loss. Sherrington showed that, in the so-called motor nerves supplying the limb muscles in mammals, from one third to one half of the fibers are afferent. If the 40 per cent reduction of ganglion cells in these experiments which are attributed to muscle loss can be taken as an index of the proportion of proprioceptive neurons normally present in the ganglia, it would indicate that the number of afferent fibers from the muscles in *Amblystoma* is of similar magnitude to that found in mammals.

WYMAN, Boston.

HYOSCINE IN POSTENCEPHALITIS LETHARGICA. P. K. MCCOWAN, J. S. HARRIS and S. A. MANN, Brit. M. J. **1**:779 (May 1) 1926.

In attempting to determine why scopolamine (hyoscine) was beneficial clinically in parkinsonism following encephalitis, the authors gave 50 Gm. of dextrose with 1/100 grain (0.6 mg.) of scopolamine to a group of eleven normal persons and determined the average blood sugar tolerance in the group. They then gave the dextrose alone to a group of patients showing parkinsonism after encephalitis and determined the sugar tolerance; about twenty-four hours later they repeated the test but gave in addition 1/100 grain of scopolamine to each patient. They found that the blood sugar curve in both the normal and the postencephalitic parkinsonian cases showed a slower initial increase, a delayed fall of the curve and sometimes a secondary rise. In explanation of their results, the authors state that the main effect of scopolamine on the blood sugar is depression of the glycogenolytic reaction and a variable glycogenetic response. These parasympatheticomimetic drugs give rise to inhibition of the external secretion of the pancreas and general arrest of the secretions of the alimentary tract. Inhibition of the external secretion of the pancreas would lead to impaired glycogenesis and a blood sugar curve showing sustained hyperglycemia. This, however, is not evident in blood sugar curves with scopolamine; but with general arrest of the alimentary secretions, the alteration in the blood sugar curve may find explanation either in diminished or retarded rate of absorption of the sugar from the intestines and a possible increased activity of the internal secretion of the pancreas.

POTTER, Akron, Ohio.

GIANT NERVE FIBERS OF THE EARTHWORM. H. B. STOUGH, J. Comp. Neurol. **40**:409 (June 15) 1926.

Many worms possess a system of giant nerve fibers running the length of the body which have been shown experimentally to transmit the impulses which cause contraction of the entire body, as happens when an earthworm suddenly darts back into its burrow. Their rate of conduction is rapid. Each

of the fibers consists of a large number of closely applied parallel axons, each of which arises from its own cell body. These axons do not run continuously throughout the length of the worm, but are strictly segmental. In each segment the cells are repeated, and the axons of the cells do not extend farther than the length of a single segment.

Each segmental element of the system of giant fibers is separated from the one in the next ganglion by a partition or septum, which is a membrane of lipoid character, is synaptic in function, and may be designated as a multiple synapse. The two elements that are in contact at a multiple synapse react differently to stains. This is shown by the darker shade imparted to one of the elements and represents a chemical difference between the protoplasms on either side of the septum. This darker shade does not cross the septum and always occurs in the outer element of the multiple synapse. The differential staining is exactly correlated with the probable direction of transmission over the giant fibers. The neurons composing the giant fibers are associated segmentally in netlike combinations, and each combination is in synaptic relation with ones of similar nature in contiguous ganglia. HERRICK, Chicago.

FRACTURE OF THE SKULL AND EXTRADURAL HEMORRHAGE WITH SYMPTOMS OF HYPOTENSION. S. SMITH, Brit. M. J. **1**:556 (March 27) 1926.

The author gives a case history and describes a man, aged 26, who was injured and taken to the hospital on November 27. Examination revealed signs of cerebral hemorrhage, and lumbar puncture gave a blood-stained spinal fluid under increased pressure. Punctures on the four following days showed progressive diminution in the pressure without clinical change. On the twelfth day, the man was able to speak, but on the thirteenth day he developed a rapid pulse and respiration, with a blood pressure of only 110 mm. of mercury; he died three days later with no signs of paralysis. Necropsy revealed laceration in the skull over the right parietal eminence and a fissured fracture extending over the petrous portion of the temporal bone through the sella turcica into the left middle fossa and forward to the posterior wall of the right orbit. There was rupture of the posterior branch of the middle meningeal artery with an extradural hemorrhage, 7 cm. in diameter, which caused flattening of the cerebral convolutions beneath it. There was also a clot about the base of the brain involving the outgoing nerves and the pituitary body. There was gross injury to the left inferior frontal pole and the superior gyrus of the temporal pole. The absence of clinical signs of pressure with this amount of extradural hemorrhage is unusual.

POTTER, Akron, Ohio.

ON THE OCCURRENCE OF ABNORMAL DEPOSITS OF IRON IN THE BRAIN IN PARKINSONISM WITH SPECIAL REFERENCE TO ITS LOCALIZATION. JEAN LHERMITTE, WALTER KRAUS and DOUGLAS MCALPINE, J. Neurol. & Psychopath. **5**:195 (Nov.) 1924.

Examination was made of the brain in a case of Parkinson's disease in a man, aged 53, who had shown marked rigidity without tremor. No history of previous epidemic encephalitis could be obtained. Intracellular iron, normally present in the globus pallidus, was diminished in amount. It was normal in amount in the substantia nigra. Abnormal deposits of a siderophilic substance were found in each globus pallidus in the form of globules; this substance was also found in vessel walls to a lesser extent, thus resembling the deposits present in some cases of epidemic encephalitis.

The chief chemical component has been shown to be ferric salts. After the removal of the iron, a substance that does not give the characteristic reactions for calcium is left. Its nature was not determined. The siderophilic deposit was found only in the oral half of the globus pallidus in its medial and more superior parts. The authors state that they have no proof that these deposits play any part in the symptomatology of the disease. The cells of the globus pallidus were reduced to half their normal number, and a definite bilateral lesion was present in the substantia nigra.

FAVILL, Chicago.

THE AFFECTIVE STATES IN LILLIPUTIAN HALLUCINATIONS. RAOUL LEROY, J. Ment. Sc. **72**:179 (April) 1926.

This paper is presented by a Frenchman to British physicians. It is strange, as the author remarks, that these curious psychosensory disorders have been studied little in the nation that produced "Gulliver's Travels." The affective state concomitant with these special hallucinations is much emphasized. The first clinical examples are accompanied by euphonia, and in several instances are preceded or followed by fright, with ordinary hallucinations. In one observation the small personages went quietly about housework when the patient was amused by their appearance; but they seemed to be astonished when the patient began to feel how strange they were, and fled in terror when he became alarmed at their actions. Other clinical examples are accompanied by fear. In all cases the mood determines the kind of hallucinations, so that at one time come charming, attractively colored people and scenes and at another black devils. The mechanism of production seems to involve dilatation of the peripheral vessels.

BOND, Philadelphia.

BLOOD SUGAR STUDIES IN ENCEPHALITIS LETHARGICA (EPIDEMIC ENCEPHALITIS). P. C. MCCOWAN, J. S. HARRIS and S. A. MANN, Lancet **1**:802 (April 17) 1926.

The authors report the results of studies of the blood sugar in fifteen cases of late epidemic encephalitis. After twelve hours of fasting, the patients were given 50 Gm. of dextrose in 8 ounces (236 cc.) of water, and blood specimens were obtained at half hour intervals for two and one-half hours. The sugar estimations were made by the Calvert method. The authors found three types of curves. One was practically the same as the normal curve following the ingestion of a dextrose meal, except that there was a secondary rise, which reached a point nearly as high as the primary elevation. In the second group, there was a prompt rise in the curve to a high level, which was followed by a rapid fall to a point near the preliminary fasting level. The third group showed a sustained hyperglycemia of long or short duration. The authors conclude that while there is definite derangement of carbohydrate metabolism after epidemic encephalitis, as shown by the blood sugar curves, they were unable to find any correlation between the clinical picture and the type of blood sugar curve.

POTTER, Akron, Ohio.

INNERVATION AND NERVE TERMINATIONS OF THE REPTILIAN LUNG. ARTHUR C. JONES, J. Comp. Neurol. **40**:371 (April 15) 1926.

This paper is a continuation of Larsell's valuable studies of the innervation of the mammalian lung previously reported. In both the snake and the turtle, sensory terminations are present in the epithelium of the bronchi and

alveoli. There are specialized intramuscular nerve endings; these are simplified muscle spindles and are present in addition to motor nerve endings. Intrapulmonary ganglia of various sizes are located in the hilum near the bronchi. The ganglion cells are surrounded by basket-like pericellular networks which probably represent the terminations of preganglionic myelinated nerve fibers from the pulmonary plexuses. Postganglionic axons are distributed to the smooth musculature of the bronchi and lungs. The pulmonary vessels are supplied by a rich plexus of fine nerve fibers, which terminate in relation with the smooth muscle cells of the tunica media. The capillaries are enveloped by fine networks of nerve fibers which parallel them or wind spirally around them.

HERRICK, Chicago.

THE WHITTINGHAM (W.) STRAIN OF ARTIFICIALLY INDUCED MALARIA: OBSERVATIONS MADE DURING THE TREATMENT OF GENERAL PARALYSIS AND TABES DORSALIS. A. R. GRANT and J. D. SILVERSTON, J. Ment. Sc. **72**:346 (July) 1926.

The increasing number of valuable reports from Great Britain describing treatment of general paralysis by malaria is augmented by this paper describing the strain of benign tertian malaria from India that was begun in England, Sept. 8, 1922. The strain has gone through sixty cultural generations and has been sent to many English hospitals. From much clinical experience, the authors believe that from five to eight rigors are sufficient for antisyphilitic therapy and are below the danger line. Severe reactions in the form of seizures, jaundice and albuminuria are described, as well as anemia, which did not disappear with the administration of quinine. Of the 150 patients, eleven died within a month of the completion of the course of fever. Despite the number of transmissions through man, the parasite retained the form and characteristics observed in naturally infected patients. The induced malaria responded rapidly to the administration of quinine, usually disappearing entirely in three days, and relapses were uncommon.

BOND, Philadelphia.

THE PRIMITIVE LINES OF AMBLYSTOMA JEFFERSONIANUM. F. L. LANDACRE, J. Comp. Neurol. **40**:471 (June 15) 1926.

The embryologic origin of cutaneous organs of sense and cranial ganglia and the relations of these to the neural crest and general ectoderm are problems of perennial interest. There seems to be extraordinary diversity among the vertebrates in the details of this developmental history. In *Amblystoma*, Landacre describes in early stages a series of primitive ectodermal thickenings, usually transient, which antedate the appearance of the specific structures, such as the otic vesicle, ganglion forming placodes, migratory lateral line placodes, and definite lateral line organs. These thickenings occupy areas over which the migratory lateral line placodes travel and in which at a later period there are formed the specific lateral line organs. It is suggested that these transient thickenings may represent a surviving vestige of phylogenetically old lines of organs of sense on which a more recent and highly specialized system of acoustico-lateralis organs of sense has been superposed.

HERRICK, Chicago.

THE MENTAL FACTOR IN MINERS' NYSTAGMUS. H. WILFRED EDDISON, J. Ment. Sc. **72**:201 (April) 1926.

This report to the Medical Research Council is especially interesting in its discussion of psychoneuroses that have all the features of miners' nystagmus except the nystagmus. It is stated that the fact that there is constant danger in the mines is as important as that there is poor light. The tremor is considered equivalent to the tremors of the hand or leg of war neuroses. Suggestion plays a part in several ways: the eye strain suggests the local target for the disturbance; the wide advertising of the disease, especially since the institution of compensation, suggests the symptoms. Prevention should forbid the employment of persons with a psychoneurotic make-up as miners, and should provide better illumination of the coal face. Perhaps the author takes for granted prevention by increasing the safety of the miners, or regards this as hopeless.

BOND, Philadelphia.

CENTRAL NERVOUS DISTURBANCES MANIFESTED BY AN EPILEPTIC FIT. J. P. MARTIN, Lancet **1**:760 (April 10) 1926.

Martin reviews the theories of Ferrier and Jackson and analyzes the epileptic convulsion. In conclusion, he says: "I have not found any unequivocal evidence of cortical stimulation but on the contrary in the prodromal symptoms, in the unconsciousness, and in the presence of an extensor plantar response at the end of the clonic stage, I see indications of cortical inhibition; the movements during the clonic stage may be explained either by cortical or brain-stem and spinal action, but the latter explanation is much more in accordance with the other elements of the fit."

POTTER, Akron, Ohio.

THE SUDORIFIC REACTION IN CERTAIN TYPES OF PSYCHOSIS. L. D. F. CHEVENS and P. B. MUMFORD, J. Ment. Sc. **72**:331 (July) 1926.

Seventy-two patients with mental disorders were exposed to radiant heat of measured and increasing temperature until visible sweat drops appeared on the trunk. The appearance of sweat was much delayed in patients having dementia praecox, and in manic conditions it was somewhat earlier than in the normal controls. It is questioned whether this contrast is caused by alteration in the sympathetic nervous system.

BOND, Philadelphia.

THE RÔLE OF CELLS OF MEDULLARY ORIGIN IN THE DEVELOPMENT OF THE SYMPATHETIC TRUNKS. ALBERT KUNTZ, J. Comp. Neurol. **40**:389 (April 15) 1926.

The embryologic origin of the neurons of the sympathetic ganglia continues to excite controversy. Kuntz has published observations and experiments which led him to believe that most of these neurons migrate out from the spinal cord along the ventral roots and rami communicantes. His observations were controverted by Müller and Ingvar, and in this paper Kuntz presents additional experimental evidence in support of his position.

HERRICK, Chicago.

GENERAL PARALYSIS AND THE TREATMENT BY MALARIA FEVER. A. R. GRANT and J. S. SILVERSTON, J. Ment. Sc. **72**:192 (April) 1926.

Reports continue to come from English hospitals about experience with the malarial treatment of general paralysis. Special points include the successful treatment of an incontinent patient with a bed sore and the death in a case of juvenile general paralysis. The authors used only pure tertian parasites in carefully identified strains, and allowed in women only two thirds of the rigors that the average male patient was allowed. The rate of recovery in men was 26 per cent, but in eleven women there was no recovery. The easy going temperament of the successfully treated men was changed to a self-assertive one.

BOND, Philadelphia.

GANGLIOGLIOMA. ARMAN C. PERKINS, Arch. Path. **2**:11 (July) 1926.

Perkins describes briefly a case that is extremely difficult to classify from a pathologic point of view and suggests the name ganglioglioma. Grossly, the tumor was of an infiltrating type. Microscopically, it was made up of islands of large cells separated by much fibrous-like tissue. Many of the cells contained several nuclei and often showed amitotic division. The nuclei were vesicular. The matrix of the tumor was made up of fibrous tissue which took a deep eosin stain.

ALPERS, Philadelphia.

Society Transactions

SOCIÉTÉ DE NEUROLOGIE DE PARIS

March 4, 1926

Rev. neurol. **1**:324, 1926

PROF. A. LÉRI, *Presiding*

CERVICAL PSEUDOSPONDYLOSIS IN EPIDEMIC ENCEPHALITIS. LOCALIZED PARKINSONIAN HYPERTONIA. DR. SICARD.

CASE 1.—A boy, aged 16, in February, 1924, complained of slight fever, headache, and diplopia. This lasted two or three days and was followed by extreme somnolence, which regressed for a week and returned two or three times, terminating at the end of the month. There was complete recovery from March to May. In June he began to have sharp pains in the neck, fixity of the head and cervicohumeral rigidity. The sphenoid sinus and the eyegrounds were normal. Nothing was found by roentgenography of the neck. The cerebrospinal fluid was normal. The tendon reflexes of the upper and lower extremities were exaggerated, but without true pyramidal signs. A competent orthopedist made a diagnosis of cervical Pott's disease in an encephalitic patient. A brace was applied for two months, but the pains persisted more markedly than without the brace.

Since 1924, the neck has regained a certain mobility and the hypertonia has improved, particularly during the summer while the patient was in the country. Now, only at times there is a slight fixity of expression and some reduction in facial mimicry. There is not any clinical or roentgenologic sign of spondylitis or articular rheumatism.

CASE 2.—A man, aged 22, had slight disturbances in vision with diplopia, in 1922; during the following week or ten days he had violent cervicoscapular pains, extreme cervical rigidity, with difficult mobility of the upper and lower limbs. The temperature was practically normal. The clinical picture was that of a subacute cervical arthritis. The cervical rigidity, immobilization of the upper end of the vertebral column, lasted from March to November and resembled that of Pott's disease, but the roentgenograms were always negative. Certain signs of facial hypertonia and especially abnormal hypersomnia which were present in September, 1922, left no doubt as to the diagnosis of "neuraxitis." Since then the general course has been favorable. The patient has been able to resume his social and professional life. The muscular rigidity is absent, and the cervical mobility has become practically normal.

CASE 3.—A boy, aged 11, in March, 1925, had lassitude without abnormal somnolence, certain disturbances of vision, not diplopia, but rapid fatigue of vision in reading and tics of the eyes. The mother said that the child rolled his eyes rhythmically almost constantly during a certain period. At the same time the patient, on returning from school, would throw himself on a couch, showing the necessity of lying down. By July, 1925, tics and grimaces became more frequent. He sucked his lips. Finally in the third stage, by September, 1925, mild evening temperature, rigidity of the muscles of the neck, pain on vertebral percussion, impossibility of flexion or movement in the cervical

spine, and finally symmetrical atrophy of the muscles of the shoulder girdle and upper limbs gave rise to the picture of radicular degeneration of scapulohumeral type. The tendon reflexes of the limbs, especially those of the lower limbs, are exaggerated, but without sign of pyramidal disease; clonus, Babinski and Mendel signs are absent. Walking is not spastic. There are no disturbances of sensibility in either limbs or face. The sphincters are normal. Electrical tests show quantitative disorders only in the muscles of the shoulder girdle and upper extremities without reaction of degeneration. Roentgenograms never have shown any bony lesion. During the last few weeks the child has improved spontaneously. The evolution of this syndrome seems to fit in well with "neuraxitis epidemica." The cervical localization with rigidity gives a peculiar aspect to this case resembling Pott's disease.

AMYOTROPHIC LATERAL SCLEROSIS WITH INTENSE CONTRACTURES OF EXTRAPYRAMIDAL TYPE. DISCUSSION OF ITS ENCEPHALITIC ETIOLOGY. DRS. GUILLAIN and ALAJOUANINE.

Along with cases of amyotrophic lateral sclerosis, in which the anterior horns are affected, giving a poliomyelitic syndrome, there are forms in which the more or less marked contracture with exaggeration of tendon reflexes indicate affection of the pyramidal tracts. The contracture is usually of classic character, but there are different types, an example of which we are presenting here. In addition to a typical pyramidal element, pronator reflex and synkinetic reinforcement, in this case there is a contracture which is typically extrapyramidal in character. A plastic hypertonia with peculiar muscular movements and tonus, cogwheel phenomenon and exaggeration of postural reflexes are present. This peculiar type of contracture in amyotrophic lateral sclerosis, as well as certain phases in its onset and evolution, allow us to suggest the hypothesis of an encephalitic etiology.

This woman, aged 38, shows bilateral Aran-Duchenne atrophy with claw hand and exaggeration of tendon reflexes, especially in the upper limbs. There is marked contracture in the same limbs, with difficulty in deglutition and phonation and clonus of the jaw. This syndrome began a year ago with the appearance of formication in the fingers and progressive limitation of movements in the right hand. Two months later there was progressive atrophy of the muscles of this hand, and the patient noticed rigidity of the whole upper limb. Later, the disease began in the left arm. During the past six weeks slow nasal speech and difficulties in swallowing have been noticed. The appearance of Aran-Duchenne atrophy is now quite marked. The upper limbs are in semiflexion, with exaggerated pronation of the forearm and wrist. The atrophy does not extend up beyond the hands. There are no fibrillary twitchings, except in the thenar eminence and in the first interosseous space. Pressure over the muscles is painful, and there are cramps in both upper extremities. Contracture is more marked on the right side. Muscular power is much diminished throughout, affecting particularly the flexors. During voluntary movement there appears a sort of rhythmic tremor, which is not found during rest. In the lower limb atrophy or modification of power are not present, although the patient recently has complained of temporary weakness in the right leg and there are slight signs of contracture. Tendon and periosteal reflexes are markedly exaggerated in the upper limbs with diffusion of the response. They are active in the lower limbs. Clonus is not present. The plantar reflexes are in flexion on both sides. There is slight atony in the lower half of the face. The nasopalpebral reflex is lively. The masseter reflex is exaggerated and fre-

quently gives rise to clonus. Speech is slow, nasal and slurred. The palate contracts well and its reflex is normal; nevertheless liquids return through the nose and the patient sometimes chokes in swallowing solid food. The tongue is normal. Electrical examination shows partial reaction of degeneration in the muscles of the hand and forearm, with variable chronaxia. Certain fibers have increased chronaxia with mild galvanotonus indicating degenerative processes; other fibers in the same muscles have diminished chronaxia like those in cases of central rigidity. Lumbar puncture and Wassermann reactions are entirely negative. The facts worthy of attention are: the character of the contracture of the upper limbs, and the existence of a probable attack of encephalitis before the onset of this syndrome.

The contracture is equally important with the atrophy at the shoulder. It is more pronounced at the root of the limb. It is less marked but still intense in the elbow and the wrist. The attitude of pronation is resumed when the arm is left to itself. This contraction is exaggerated when the patient reinforces the movement by squeezing the hand on the opposite side. In other words there is a synkinesis of coordination. However, in addition to this pyramidal contracture, there is an extrapyramidal contracture. This is revealed when the various segments of the arm are moved, particularly the elbow. The extension takes place in the typical cogwheel manner seen in the parkinsonian state. The postural reflexes in the wrist and elbow are exaggerated. The contracture also is marked in the neck, whereas it is mild in the lower extremities.

A little more than two years before the onset of the present illness, the patient had an attack of illness beginning with sharp pains of pinching or tearing character in the neck and scapular region, in the intercostal area and in the upper limbs. She had insomnia for nearly two months. Diplopia was not present, however. After this there was considerable asthenia, but nothing notable in the interval. However, when the amyotrophy began, there were disorders in sleep, such as somnolence during the day, which the patient could not resist, accompanied by disagreeable sensations and by depression. The presence of the disorders of sleep and pains have made us believe in the encephalitic origin of this case of amytrophic lateral sclerosis.

JACKSONIAN EPILEPSY: TUMOR OPAQUE TO THE ROENTGEN RAYS. O. CROUZON and CLAIRE VOGT.

A woman, aged 26, has had attacks of jacksonian epilepsy since the age of 9. At first they came every month, but recently they have been coming every two months. The crises are always preceded by a motor aura, that is, rigidity of the left leg, some twitching in the left arm and occasionally a little diplopia. The aura lasts five minutes. It is followed by a fit which always begins by forcible flexion of the fingers of the left hand in the palm, then the face, and finally in the left leg. The convulsion lasts five minutes. The patient does not lose consciousness. She complains of severe pains in the convulsed limb. Sight is disordered. Occasionally she presents a mild confusion. During the early period, attacks were severe and lasted several hours, but they have become less marked recently. On the other hand, there is mild continuous unlocalized headache. Up to five years ago the crises were followed by vomiting, but since then there has been only nausea. Aside from these attacks the patient presents certain modifications that resemble epileptic equivalents. Suddenly, at times, she is seized by unreasoning fear, accompanied with anguish, compulsions, sweats. When these frights come on during the day they manifest themselves by small fugues; for instance, the patient runs out of the room.

The crises last a few seconds and cease abruptly. The patient is quite forgetful. Intellectual work is difficult; even at school, before the beginning of the convulsions, she learned with difficulty. On examination the patient uses the left hand less than normal. She claims to be clumsy with this hand. There is slight reduction in the power of the flexors. The tendon reflexes are more lively on the left side. Clonus is not present. On warming the feet there is extension of the great toe on plantar stimulation. There is a distinct sign of combined flexion of the thigh and trunk. Aside from these signs, there are some "cerebellar" symptoms in the left upper extremity, but these are perhaps related to the pyramidal condition. The index finger is brought to the nose slowly and interruptedly. There is adiadokokinesis. The fingers become more and more spread; the movements are slow. The patient says that she lets objects fall when she has a fright. Superficial and deep sensibility are normal. There is nothing abnormal in the cranial nerves. Spinal puncture gives only negative results. In the roentgenogram there is a black shadow 5 cm. long and 2 cm. high, which is markedly irregular. This is 3 cm. from the vertex of the skull. The anterior portion is 5 mm. from the median line. There is thus a calcified tumor, deeply situated, which appears to be localized in the centrum ovale close to the right lateral ventricle. The origin of this tumor is difficult to determine. The patient was delivered at birth by forceps, and had a scar in the right temporal region.

In 1925, she was operated on for a hydatid cyst of the liver. Syphilis is practically ruled out. The tumor may be a calcified hematoma caused by the obstetric traumatism, or it may be a psammoma springing from the plexus or a glioma that had regressed and become calcified. The tumor is evidently not progressive, since roentgenograms taken several years ago and those of today are indistinguishable. The case is also interesting because this tumor, although situated in the center of the brain, brought only jacksonian attacks for seventeen years.

DISCUSSION

DR. BARRÉ. A calcified tuberculoma might be found; an operation at this depth is possible but hardly indicated.

DR. SOUQUES: The tumor is too deep in this case to be reached.

DR. LÉRI: Calcified tuberculomas are frequently found in the brain.

FREEMAN, Washington, D. C.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Regular Meeting, Thursday, Oct. 21, 1926

DONALD GREGG, M.D., *President, in the Chair*

DEMONSTRATION OF DECORTICATED CATS. DR. GEORG SCHALTENBRAND and DR. STANLEY COBB.

For the purpose of physiologic and pharmacologic studies of mobility we intended to repeat the old experiments of Goltz, Rothmann, Dusser de Barenne and others, who successfully removed the forebrain in higher mammals. We are especially interested in the eventual share of the striatum in mobility, and in a more exact localization of the bulbocapnine in catalepsy.

The technic of the operations is of interest because we have found it much better to operate under local anesthesia than under ether. We first give the animals a dose of bulbocapnine hydrochloride from 0.02 to 0.03 Gm. for each kilogram of weight. After about fifteen minutes, the cat becomes cataleptic; it is then placed on the operating table and shaved. The neck is first opened and small bulldog clips are placed on the carotid arteries (this part of the operation is done under ether anesthesia, as it was found that handling the vagus nerve when the animals were not thoroughly anesthetized caused death in some cases). When the carotid arteries have been temporarily closed, the animal is turned over and the head is prepared. Procaine hydrochloride, 1 per cent solution, then is injected into the scalp and epicranium, and the operation proceeds under strictly aseptic precautions. Through an enlarged trephine opening in the skull the dura is opened and the hemisphere laid bare. If the animal is to be made a "thalamus cat" the procedure is as follows: the gyrus fornicatus is split until the lateral ventricle is widely open; then the incision is carried down to the anterior edge of the cornu ammonis, along the outside edge of the lobus pyriformis and along the rest of the basal rhinencephalon, meeting the beginning of the incision approximately at right angles, so that only a thin layer of rhinencephalon remains anterior to the thalamus. With a blunt dissector the hemisphere then is raised and carefully removed. There remains only the thalamus and the basal portions of the rhinencephalon.

If a "striatum preparation" is to be made, the lateral ventricle is opened as described above and the knife circles round the outer edge of the caudate nucleus. The incised cortex is lifted carefully, and the cortex of the island of Reil is removed afterward. There then remains only the cortex in the pyriform lobe, the striatum remaining intact. After all bleeding has been stopped by placing pieces of muscle in the brain cavity, the muscles are sewed over the wound and the skin is closed with a Michel clip. About a half hour afterward, the clamps are removed from the carotid arteries. After the operation the animal remains on the operating table, restrained with head-holder and straps, for from four to six hours. This is done because of the marked motor restlessness that follows such operations. We remove only the cortex of one hemisphere at the time and wait for a few weeks before we perform the second operation. At present we have one cat alive which has been operated on bilaterally, and three which have been operated on only on one side.

The results of these unilateral decortications are as follows: Immediately after the operation there is the hyperkinesis mentioned above. Next morning, if all has gone well, the animals are able to walk, and it is then found that they circle toward the normal side; that is to say, if the right hemisphere has been removed the animal circles toward the left. This, however, only lasts for about one or two days, and usually by the third day the animals begin circling toward the side operated on. This phenomenon persists or at least lasts for two or three months (this being as long as we have observed any hemidecortications). When the animals are blindfolded, however, they immediately begin circling toward the opposite side — that is, they revert to the condition seen immediately after the operation; an animal with the right hemisphere removed, when blindfolded, will circle toward the left.

Besides these locomotor phenomena, there are changes in tone. Immediately after operation and lasting for one or two days, there is a general spastic paralysis of the contralateral legs, which are held in strong extension. Later, this weakness and extensor rigidity diminish, so that from three to four days after operation there are observable only a slight increase of tone in the con-

tralateral legs and a moderate exaggeration of the extensor posture, visible when the animal is lying on its back. This, however, can be demonstrated even from two to three months after operation. In the sensory realm, impairment of the sense of position on the contralateral side is found. This is best shown by placing the limbs in some abnormal position; the animal then is

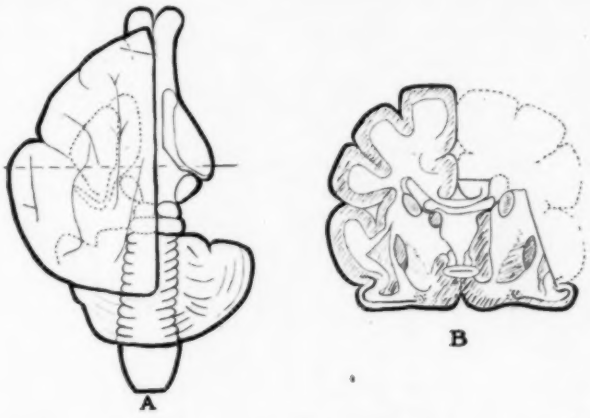


Fig. 1.—Diagram of brain remaining after unilateral operation for "striatum cat." The dotted line across the surface view (*A*) indicates the level at which the section is made illustrated by (*B*).

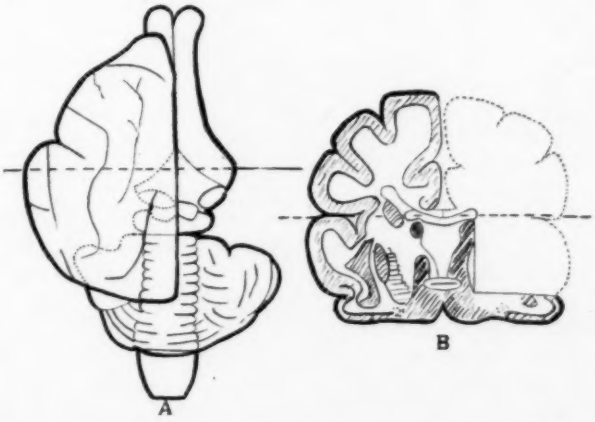


Fig. 2.—Diagram of brain after operation for unilateral "thalamus cat." The dotted line across the surface view (*A*) indicates the level at which the section is made illustrated by (*B*).

apparently unconscious of the uneasy posture and does not move. There is also impaired localization for pain stimuli. When the animals are able to run and can stand being taken outdoors where there is plenty of room, it is easily shown that they have a homonymous hemianopia in the field opposite the lesion (an animal with the right hemisphere removed would have a left

homonymous hemianopia). This can be demonstrated by calling the animal until it begins to follow you — then by walking in and out of the field of vision it is found that the animal loses track of you — it is lost while you are in the hemianopic field, whereas it immediately runs toward you when you get into the intact field of vision. A curious symptom, shown by some of the animals, was a great shaking of the contralateral legs during the first few days after operation. This was begun whenever the animal started walking, and was especially noticeable if it got moisture or dirt on its feet; it is apparently an exaggeration of normal shaking.

The first of three animals on which experiments were performed was a maltese cat, operated on Aug. 8, 1926. The right hemisphere was removed in front of and above the thalamus. The animal could then be referred to as a "right-sided thalamus cat." Immediately after operation the body arched to the left, the convex side being to the right. A few days later, when convalescent and walking about, it circled to the right and has done so ever since. When blindfolded, however, the cat reverses the direction of circling. It still has marked extensor tone of the left legs when lying on the back.

The next cat was operated on, Oct. 1, 1926; the right neopallium was extirpated, leaving the right striatum intact. Since the operation the animal has shown changes of posture of the head. In locomotion it circles to the right, but when blindfolded circles to the left. There is hyperextension of the left legs, when it is laid on its back.

The third cat had the first operation on Aug. 4, 1926, when we removed the left neopallium without injuring the striatum. Immediately after the operation the cat circled to the right, but a few days later began circling to the left. There were contralateral hyperextension and marked shaking movements of the right legs whenever the cat began to walk. Early in September, examination showed that there was still a certain amount of right-sided hyperextension, and the cat circled to the left whenever it walked. About September 20, the animal began to look ill, and it was decided to operate and remove the other hemisphere before death. Operation revealed great hydrocephalus and some meningitis of the right hemisphere. The neopallium on the right was removed, leaving the animal a "bilateral striatum cat." It made a good recovery and shows the following important symptoms: it is able to recognize smells and eats spontaneously, but in a reflex way that causes it to eat too much; the gait is somewhat shaky and occasionally there are exaggerated shaking movements of all four legs, as if the animal is trying to shake off moisture or some obnoxious object attached to the paw; it walks easily, often bumping into objects as if blind, and is hyperkinetic. The pupils react well to light, and the cat shuts its eyes when a bright light falls suddenly into them. It is now three weeks since the operation, and the animal appears to be progressing well. When given bulbocapnine it gives a normal cataleptoid reaction.

Other cats that we have operated on unfortunately died. Two of them were thalamus cats and survived the second operation; they appeared much like the one described, but contracted pneumonia and died. Altogether, we have observed seven unilateral cats. We intend to make the remaining unilateral cats into bilateral thalamus or striatum animals.

DISCUSSION

DR. H. C. SOLOMON: If the visual cortex is removed on one side without other cortical disturbance, will the animal tend to move in a circle as do the animals with half the cortex removed?

DR. COBB: I believe so; I am not sure. We ought to do that as a check.

DR. SOLOMON: Has any other work been done on hemidecortication?

DR. COBB: There have been, in the history of medicine, various decorticated animals that were kept alive after operation for a considerable period and really showed the chronic symptomatology. I have listed these in chronologic order, as follows:

Chronic Decorticated Animals

1825

Magendie	goat	
Goltz	dog	Striatum
Rothmann	dog	Striatum
Pawlow	dog	Striatum
Dresel	dog	— Thalamus
Dusser de Barenne	two cats	(1 with rhinencephalon)
Karpus and Kreidel	monkeys	
Morita	rabbits	
Magnus	rabbits	
Rademaker	rabbits	

The first, reported by Magendie, was not a true chronic experiment. I mention it merely to show at what an early date physiologists began to speculate about these things. Monkeys always had shock after the operation and did not come out of it, even though they survived as long as six weeks. Rabbits and other rodents frequently have been used but are not of as much interest as the carnivora and higher mammals. Therefore, this animal is about the eighth higher mammal and perhaps the third cat to survive this operation.

DR. SOLOMON: If you only remove the motor cortex, does a paralysis result?

DR. COBB: A short one, yes.

DR. SOLOMON: Is there paralysis after the removal of the hemicortex immediately on recovery?

DR. COBB: There is some weakness for about forty-eight hours; after that there is nothing.

DR. SOLOMON: Is that less than if the motor cortex had been removed?

DR. COBB: About the same.

VACCINE THERAPY IN MULTIPLE SCLEROSIS: PRELIMINARY REPORT. DR. HENRY R. VIETS.

In July of this year at the Massachusetts General Hospital, treatment of cases of multiple sclerosis with typhoid vaccine was started. This type of treatment has been used at other clinics since 1918 with fair results. In 1922, Karl Crosy reported on the treatment in fifty-nine cases (*Jahrb. f. Psychiat. u. Neurol.* **42**:19, 1922). He found improvement in about 30 per cent. In 1924, MacBride and Carmichael treated seventy patients, with some improvement (*Lancet* **2**:958, 1924).

Six patients have been treated with at least one course of vaccine therapy. The courses have consisted of eight treatments, once a week, and the dose has averaged from 0.1 to 3.2 cc. when given subcutaneously, and from 0.025 to 0.75 cc. when given intravenously. The vaccine used was the triple typhoid vaccine from the Massachusetts State Board of Health, 1 cc. being equal to 2,500,000,000 bacteria. The average age of the patients was 25 years, and the average age at onset, 20.6 years. All patients suffered from spastic paraplegia, and all but one had lost the abdominal reflexes. Tremor was present in all. One had speech defect, one sphincter weakness, one visual

defect, and three had nystagmus. Three had progressed steadily, and three showed irregular progress of the disease. Chills and fever accompanied nearly all the injections, especially those given intravenously. The fever rose in from four to six hours to 101 or 102, subsiding rapidly. Definite ill effects from the treatment were not seen. Four patients were thought to have improved and one to have improved markedly; two others had less numbness but otherwise showed no change.

DISCUSSION

DR. H. C. SOLOMON: I have seen several of the patients in the outpatient department that have been given this course of treatment. Of these, three have reported marked improvement of the sensory symptoms. In my experience most cases of multiple sclerosis show sensory symptoms and that is the first thing the patient complains of. In these three cases the patients have reported complete remission of the sensory phenomena. One patient said he had been cured three times previously by his family physician by some drug that worked within twenty-four hours and completely cured his sensory symptoms. The other two patients seemed to be enthusiastic about what had occurred. This treatment has been used elsewhere for a considerable length of time. In New York many types of nervous diseases have been treated with typhoid vaccine. As to the frequency of treatments with typhoid vaccine, it can be given every other day. I have given typhoid vaccine to patients who have had malaria treatment every day for several days to produce a chill. The chill lasts a short time and does not leave any ill effects, and that is the end of the whole situation as far as typhoid is concerned.

THE NEUROPSYCHIATRIC PROBLEM OF THE U. S. VETERANS' BUREAU. DR. A. H. PIERCE.

In considering the neuropsychiatric problem of the Veterans' Bureau, I shall cite some historical and statistical facts. From the experience of the Allies, it was known that a large proportion of the casualties would be from neuropsychiatric disease. Therefore, on entering the war, the United States Army developed a neuropsychiatric corps that sought to eliminate, before entrance into military service, such men as were unfit from a psychiatric point of view, and to care adequately for cases developing during service. As anticipated, psychiatric cases developed rapidly, and the federal government was forced to throw this tremendous burden on the U. S. Public Health Service, which was better prepared than any other department to attempt to cope with the situation. However, its facilities were wholly inadequate, and dependent as it was on legislation by Congress to provide suitable hospitals and expert care, it could not meet the emergency as it should be met. The utilization of all available government hospitals and the leasing of civil or private institutions had to be resorted to pending the erection of special hospitals. The personnel problem was met by putting into the Public Health Service a large number of reserve officers, principally from the emergency medical officers of the U. S. Army.

With the continual increase of ex-service men requiring medical care, it was decided in 1921 to amalgamate with this work the Bureau of War Risk Insurance and the Vocational Rehabilitation Service. Accordingly, the U. S. Veterans' Bureau was formed, with a director appointed by the President and directly responsible to him.

The following figures give some idea of the magnitude of the activities of the Veterans' Bureau: 1925, total disbursements more than $393,000,000;

1926, total disbursements more than $400,000,000. Of these amounts, $40,000,000 was for the maintenance of hospitals.

1925—Compensated cases	211,644	
1925—Monthly disbursements of these		$8,000,000
1925—Personnel in Veterans' Bureau	27,622	

Compensated Cases:

Neuropsychiatric disabilities	21 per cent (44,800 plus)
Tuberculous disabilities	21 per cent (45,000 plus)

In 1925, 44 per cent of all hospitalized patients were neuropsychiatric, there being 12,139 at the end of the year in this group.

1925—Inpatient days	5,787,170	
Average per capita cost		$4.04
Examinations of ex-service men	1,144,330	
Men listed in Vocational Rehabilitation	330,000	

On June 30, 1925, insurance records were maintained for 552,340 veterans carrying $2,865,028,729 in insurance.

As to the character and cause of these neuropsychiatric disabilities: At first, the preponderance was in the psychoneurotic group and later in the psychotic group. Gradual elimination from hospitals of the psychoneurotic patients, by means of outpatient departments and the agency of the social service, has been accomplished largely. Congressional acts which practically placed a premium on a man remaining in the hospital have been changed, or amended. When a man's compensation is continued while he is hospitalized, and ceases or is cut down on dehospitalization, it is difficult effectually to get him on his feet again. The psychotic group, in which the preponderance now is, comprised practically all variations of mental disease but today, in the main, consists of the deteriorating psychoses, the schizophrenic group.

With regard to the origin of these cases, a certain small number, relatively speaking, had a traumatic neurosis (so-called shell-shock cases). The much larger proportion consisted of cases in which the strain of military life, either in combat or not, was borne poorly. My own belief is that the chief cause for these nervous and mental breakdowns was the strain of adaptation. It is probably true that many insane veterans would have become so if they never had entered the army, but it probably would have been under some stress or strain that they were unable to handle mentally. I give mental stress as the chief cause, but this does not preclude other causes of perhaps minor importance. I have not touched on the question of a physical basis for mental disease, because, in the absence of such evidence, one seeks the cause in the psychic realm.

The important point now is reached. What can be done for these men, and what is the Veterans' Bureau accomplishing?

What can be done, under present limitations of medical knowledge, may be summarized under the following headings:

Conduct control

Physical examination and treatment:
- Physiotherapy (broadly speaking)
- Drugs (when indicated)
- Occupational therapy

Mental treatment:
Occupational therapy
Recreation
Psychanalysis (broadly speaking)

The bureau is assisting, by means of hospitals and outpatient departments and by financial assistance, the psychoneurotic patients to get on their feet. Vocational training has been of considerable help in the work, although the psychoneurotic patient is not a particularly encouraging subject.

The chief problem in the hospitals treating neuropsychiatric cases is the care of patients with psychoses. There are sixteen bureau hospitals of this type, twelve of which are of practically new construction. Six have been finished and opened within the last two and one-half years. These hospitals are caring for 7,744 patients at present, and have a total medical personnel of 236, with a total personnel of 4,216.

The hospital at Northampton is a fair example of these newer hospitals. The following statistics apply to it:

Physicians, including administrative officers	9
Consultants	6
Graduate nurses	25
Technical personnel (occupational therapy, physical therapy, roentgenography	14
Other personnel	186
	241
Patient population	433
Graduate nurses	25
Nursing attendants	76

The hospital reservation comprises 282 acres, and is situated on a hill at an elevation of 425 feet, 100 feet above the highway. There are twenty-three buildings, with two more to be added during the present year. Nearly all are of brick and concrete and are fireproof. The main group of buildings is at the top of the hill, enclosed by a wire fence, and consists of the administration building, with the administration offices in the center and admitting wards, infirmary ward, continued treatment ward, and physiotherapy department in its wings. In the clinical corridor of this building is a laboratory, large general operating room, sterilizing room, and etherization and recovery rooms. There is also a large dental clinic, ear, nose and throat room, and roentgen-ray department. All departments are well equipped with every modern means of caring for the bureau beneficiaries. In the basement of the administration building is an issue room, various store rooms and occupational therapy rooms. To the rear of the administration or main building are grouped six other ward buildings, the kitchen and mess halls, as well as the attendants' quarters and the new recreation building. These buildings are arranged about an oval, in the center of which is a fine ball field. The recreation building contains an auditorium seating 500, a large stage, four dressing rooms, social room, smoking room, library and pool room. In its basement are bowling alleys, gymnasium and swimming pool with shower baths.

Comparatively few ward windows are grilled. All buildings are heated from a central heating plant, and steam is supplied to the larger kitchens. All other cooking is done by electricity. All the buildings in the main group are con-

nected by covered walks. The water supply is from Northampton city main, and sewage disposal is into the city system. The total cost of the plant at present is about $3,000,000.

The hospital is licensed by the State Commission of Mental Diseases by authority of an act of the Great and General Court passed in 1924, so that it must comply with both the regulations of the Veterans' Bureau and the requirements of the state laws concerning the insane.

Because of certain technicalities the hospital can receive only patients who are insane and who are receiving compensation. Most of the patients are transferred from various state hospitals in New England, which means that 75 per cent of the load is of deteriorated cases—patients who had been in state hospitals as a rule for years, and in whom recovery can hardly be expected. Of the remaining 25 per cent, fully one half are suffering from mental disease in which deterioration is to be expected. A patient is not charged for his hospital care, but each must supply his own clothing if financially able. Almost all are able, because, in addition to care, they receive $20 a month for clothing and luxuries. This is called an institutional award and represents $20 of the $80 or more which each totally disabled man would receive. If the patient has dependents, the remainder of the $60 is paid to his guardian. If the patient recovers, the remainder is payable to him.

As to treatment and results, so far as numbers are concerned, the chief medical problem is the care and treatment of chronic cases; but there is also the treatment in cases that might be considered as recoverable. In the treatment in the latter group, particular stress has been laid on hydrotherapy, occupation, detailed personal attention, and medication when indicated.

In the treatment of the first and large group, the physicians have been compelled to depend on physical and mental hygiene, which includes a reasonable institutional system of living, occupational therapy, physiotherapy and recreation. Fortunately, treatment directed to the physical and mental condition runs fairly parallel, as every physical handicap must be overcome if the maximum mental benefit is to be received. On the physical side, there must be painstaking investigation, with suitable, energetic and adequate treatment if physical disease is discovered. The most conscientious work on the part of the clinical service is necessary here, and the equipment of the hospital is practically complete for the application of every recognized means of treating physical illness.

The mental treatment falls into three divisions:

Occupational therapy
Recreation (not to interfere with occupation)
- Entertainments
- Drives
- Bowling
- Swimming
- Music
- Baseball
- Dancing

Psychanalysis

Psychotherapy is limited because the ward surgeon, burdened as he is with administrative details, etc., cannot give the necessary time.

Certain results have been secured which statistical tables cannot reflect. Obviously, the number of "recoveries" is limited, but the large majority of patients show marked improvement in such particulars as: better living habits; interest in personal appearance; improved table manners; willingness to assist in the wards; better conduct at entertainments and church service; keener appreciation of enjoyable affairs; less discontent, and more enjoyment of life with happier adaption to the surroundings as a whole. Of the total number of 600 patients thus far received, eighty-four have made sufficient improvement to remain at home, presumably making a reasonably satisfactory social adjustment, and in several instances an economic one. The remaining patients are improved as outlined above, and many are approaching a point where they can go out on a visit.

Activities of the patients about the hospital, under the direction of the occupational therapy department, not only serve to further the physical and mental improvement, but also are the means of substantial saving to the government. The condition of the grounds is rapidly improving, made possible mainly through patient labor under the direction of a landscape architect who is employed on part time. A nursery has been established; lawns have been built or completed; a sunken garden at the main gate has been constructed with plants, a cement pool and a fountain. All these activities are carried on directly or indirectly as occupational therapy projects, and though progress with patient labor is not rapid, it serves the two purposes mentioned. Other activities in which patients have been engaged successfully are: Construction of tennis courts, garages, poultry houses, piggery and ornamental fountains; brush making, shoe repairing, cleaning and pressing clothes, repairing furniture, carpentry and craft work.

The medical officers are civil service employees. The administration of the hospital is directly under the medical division of the central office of the U. S. Veterans' Bureau. Admissions of patients, except in emergency, are made under authority of the various regional offices of the bureau. New patients are held under temporary committment papers until they are examined and committed in the local district court. Examinations for this purpose are conducted by expert psychiatrists having no direct connection with the bureau. Coordination of the various bureau activities in the New England section, as well as inspections and investigations, is under the control of a chief coordinator, whose office is in New York. The financing of the hospital is under a rigid budget system.

During the last two years, great advance has been made in the organization of the medical department of the bureau. An advisory board, the so-called medical council, consisting of physicians of the highest standing in the United States, has been appointed. Research work has been undertaken and an organization built up to carry it on. The bureau has its own magazine, the *Medical Bulletin,* which is contributed to by the medical officers of the service. Every medical officer is required to contribute a paper at least yearly, and from this number are selected the articles of greatest value or of most timely interest.

In conclusion, the neuropsychiatric problem of the Veterans' Bureau is precisely the same problem that every state has to meet and has been meeting for generations. In meeting it the Veterans' Bureau has a great advantage, as it is not so limited in funds as has usually been the case with the state. I believe

the real problem now is to develop a medical personnel to secure maximum professional and scientific interest in the work. Congress has been and is doing its share; it remains for the medical officers of the bureau to spare neither labor nor pains.

DISCUSSION

DR. E. O. CROSSMAN: When I attempt to visualize the problems of the Veterans' Bureau, particularly with reference to neuropsychiatric disabilities, I realize that in Congress there are many different committees, and the Veterans' Bureau, in the psychiatric department, has many different problems. Dr. Pierce has presented the summary of the origin, progress and functions of the Veterans' Bureau in an admirable manner. Perhaps I ought to elaborate on the work a bit. It is divided into three departments—neuropsychiatric, general medical and surgical, and tuberculous or respiratory diseases. There are fifty-two Veterans' Bureau hospitals in the country; there are more than 100 clinics, and between 27,000 and 30,000 patients in the hospitals all the time. The aim in Washington has been to develop scientific medicine in every way possible, and many things have been done that I know have tended and are tending to make the Veterans' Bureau hospitals as good as there are in the country. The American College of Surgeons surveyed the hospitals about two years ago and all but four were accepted. I think all but one now are accepted by the American College of Surgeons. Dr. Pierce has spoken of various forms of treatment; the department of research, medical department, medical bulletins, etc. Our thought was that if every man was urged to write a scientific paper every year it would result in great good. It certainly has. The Veterans' Bureau has something like 1,500 full-time medical officers; between 1,600 and 1,700 nurses, and a personnel in all of about 25,000. It is a gigantic and chiefly a medical proposition. There is not a problem anywhere in the Veterans' Bureau that does not have a medical slant, and the aim has been to administer, with as much sense as could be developed, to the care of the men entrusted to us.

Before I left Washington, a committee of three, consisting of Dr. A. L. Gilchrist, colonel in the U. S. Army, Dr. Philip B. Metz of the Department of Research in the U. S. Veterans' Bureau at Washington and Dr. A. K. Krause of the Johns Hopkins University at Baltimore, was appointed to study and investigate the residual effects of war gases on the human body. This investigation will prove, I believe, one of the most valuable contributions to medicine that has been developed by the Veterans' Bureau. One had heard so much about men being gassed, with a great lack of scientific knowledge to date, but the time and material now available seems suitable for definite and dependable report to the profession.

There were cases without number with half a dozen different diagnoses. There must be a definite diagnosis because it has to do largely with the vital question of compensation. The director authorized a diagnostic clinic in Washington, accommodating about 250 patients, and that hospital is manned by part of the staff of Johns Hopkins University and the remainder from Washington; men are sent there from every area in the East. That has been important, because when a man goes there he has every facility known to science for the study and diagnosis of his case, and when a conclusion is reached it is final so far as the diagnosis is concerned. A small diagnostic

clinic also was started in Cincinnati with twenty-eight beds in conjunction with the Cincinnati General Hospital. Before I left, it had practically been decided to recommend another diagnostic clinic at Palo Alto, California, in connection with the hospital there.

One might ask how many of the men in the service really have applied to the Veterans' Bureau. I have not the figures available, but not long ago there were treated in one month at the outpatient clinics about 105,000 different people; that is, in addition to the work in the hospitals. The Veterans' Bureau is certainly the biggest medical organization in this country.

Dr. Pierce has spoken of the expense. You all know that there are three hospitals in Massachusetts; one at Northampton, the West Roxbury Hospital, and the hospital for tuberculosis at Rutland, the latter accommodating 400. The last time I checked up there were 266 patients at Rutland; there are 270 at West Roxbury and 433 at Northampton. All the Veterans' Bureau hospitals in New England are in Massachusetts. There were something like 200,000 men inducted into the service from Massachusetts and, you will recall, at first the only hospital here was the one at West Roxbury. The hospital at Northampton was built and that at Rutland was remodelled. The district office in Boston had supervision over all New England except Connecticut. Decentralization took place, and now each state has a regional office and clinic. New York has two: one in Buffalo and one in New York City. Pennsylvania has one in Philadelphia and one in Pittsburgh, but, for the most part, the men are cared for in their own states.

Dr. Pierce has stated that the Veterans' Bureau offers the greatest medical opportunity for research, investigation and scientific work that ever has been offered to the medical profession, and certainly if there is a better understanding of the work that is being attempted by the government throughout the country I am sure it will be of great benefit to the profession and to the men who are unfortunate enough to be turned over to our care.

Dr. George Clymer: Dr. Pierce and Dr. Crossman have given you a good outline of the work of the Veterans' Bureau, and I merely want to say one word in testimony of the tremendous improvement in the work that is being done in the Veterans' Bureau hospitals. I have been fortunate in having had an opportunity to see the development of this work as, in 1919, I began as a visiting consultant at the East Norfolk hospital to which ex-service men who had epilepsy and various sorts of convulsive and hysterical attacks were sent. Soon after the hospital at West Roxbury was opened, I added that to my route, and since the Northampton hospital opened I have been going there also. In the early days the work done in the first two hospitals was somewhat rudimentary. The records were poor; diagnoses were made, but not a great deal was done to try to help the patients. There were a great many psychoneurotic patients at that time, but little attempt was made at constructive therapy. Now, at West Roxbury and Northampton there are good records and excellent conditions otherwise.

There are still many problems in regard to the diagnosis and the treatment in these cases. One group that still gives much trouble has not been spoken of. This is the group of constitutionally inferior individuals—the men who do not fall into the group of psychoses or psychoneuroses. They do not make a good adjustment in the community, either socially or occupationally. They are sent to the hospitals because of various symptoms and because of maladjust-

ment in their communities. After a while they are discharged, because the hospitals feel that they cannot do anything more for them. In the course of time they come back again. It seems to me that this is one of the problems that still confronts the Veterans' Bureau.

In this community there is another problem that may not be as great as it seems to me, but about which I feel strongly; it was emphasized only a short time ago in the case of a man who had been a patient at the West Roxbury hospital where his mental state had been diagnosed as paranoid dementia praecox. The West Roxbury hospital is not licensed to accept committed patients. He could not be committed there, and in the course of time his guardian and his family insisted that he be taken from the hospital. He was discharged against the advice of the officials, who were powerless to hold him legally, and recently ran amuck, seriously wounding one person and killing himself. It seems that this definite problem is not being satisfactorily met by the Veterans' Bureau in this community.

Dr. H. C. Solomon: While the Veterans' Bureau hospitals are good and have improved tremendously in the last several years, the fact still remains that they are being compared with the state hospitals, and that is wrong. The state hospitals are doing the best work that it is possible to do with little money. Government hospitals are run on a more liberal allowance, but they do not get enough money to take care of the patients as well as they might be taken care of. Every time one speaks of adding a man to the medical staff it is looked on as though it meant fifty men because there are fifty hospitals. If one asks for $1,000 for a medical library, the government thinks of $50,000. The state hospital is based on a little better than $10 per capita as the ideal; in the government hospitals the ideal is about $20, but that is not sufficient to secure good personnel. One cannot do a great deal of personal work with patients when he has eighty or more under his charge, when three hours a day are devoted to conferences and five hours to work on papers.

Dr. Donald Gregg: Why was it that the peak of the load was understood to be ten years after the war? Am I correct in thinking that the peak of the load would fall at that time?

Dr. Pierce: I cannot tell you exactly about that. According to the Acts of Congress, any man who developed a neuropsychiatric disease previous to Jan. 1, 1925, was considered a case with the connected service. The policy of the government from the start was to take care of men who were suffering as a result of war service. I cannot tell you exactly how it was computed, but it was fairly obvious that there would be a great many cases.

Dr. Gregg: Is the load decreasing now?

Dr. Pierce: It is still increasing. I do not know when it will stop increasing. For instance, among the 433 patients there are only fifteen or sixteen cases of general paralysis and four or five of neurosyphilis. Dr. Solomon speaks of ideals. I think we have certain definite ideals, and as emphasizing what he said it strikes me that the amount of money that can be spent in ordinary medical and surgical work in hospitals is almost unlimited. Why should one discriminate against those mentally ill? Perhaps because in the first two instances one sees definite, concrete results, while in patients mentally ill they are more difficult to attain.

Some Remarks Concerning the Platinum Chloride Method of W. Ford Robertson for the "Mesoglia." Dr. Percival Bailey.

Note: This paper was presented at a previous meeting of the society and is now published for the first time.

The recent researches of del Rio Hortega have called attention again to certain small cells in the brain, which lie along the long fiber tracts, near the blood vessels and at the bases of the large nerve cells. Hortega calls them oligodendroglia, and they have been designated variously in the literature as rounded cells (Eisath), pre-ameboid cells (Rosenthal), cuboid cells (Cerletti), and were included by Cajal among his "third elements." Hortega has devised a method for impregnating these oligodendroglial cells, which gives good preparations at times but is uncertain. I was therefore pleased to find a method described by Robertson (Hall and Herxheimer: Methods of Morbid Histology, Philadelphia, J. B. Lippincott Co., 1905, p. 205) which seemed to give much more satisfactory preparations.

In actual practice, however, I found this method far less easy than I had supposed. In his first publication (*Scottish M. & S. J.* **4**:23, 1899), Robertson says he used platinum bichloride (or dichloride, $PtCl_2$); this is insoluble in water, so it certainly was not this salt that he used. In a presentation of his microscopic preparations before the autumn meeting of the Scottish Division of the Medico-Psychological Association of Great Britain and Ireland, Nov. 16, 1899, Robertson said he used platinum bichloride, but wrote $PtCl_4$ in the report published later (*J. Ment. Sc.* **46**:200, 1900). In his textbook, published in 1900 (Pathology of Mental Diseases, Edinburgh, Clay, 1900, p. 28), he again writes platinum bichloride, and adds that it is obtained in gram tubes and must not be confused with potassium chloroplatinite. This made me feel that he probably used the ordinary platinum chloride of commerce which is hydrochloroplatinic acid ($H_2PtCl_6 + 6H_2O$), and a reagent commonly employed in histologic procedures. I wrote first to Robertson's son, W. M. Ford Robertson, who kindly informed me that his father had obtained the reagent from Harrington Brothers in London. I then wrote to this firm asking them to send me the same salt that they had supplied to Robertson. They sent me hydrochloroplatinic acid. I (Bailey and Hiller: *J. Nerv. & Ment. Dis.* **59**:337, 1924) therefore took it for granted that this salt was the one which Robertson erroneously had called platinum bichloride.

Using the salt sent me by Harrington Brothers, I obtained impregnations of the oligodendroglia, but they were imperfect. I wrote again to W. M. Ford Robertson asking him to send me some of his father's preparations. He was so kind as to send me an entire set which his father had used for a demonstration. In the notes accompanying this demonstration set Robertson had written again $PtCl_4$.

The preparations are so beautiful I could not refrain from showing them, with the hope that some one else will try to reproduce them. In this connection it has occurred to me that Robertson after all, really may have used platinum tetrachloride ($PtCl_4 + 5H_2O$) which occurs in red monoclinic crystals and is soluble in water, or even chloroplatinous acid (H_2PtCl_4), which is prepared from the potassium platinochloride, against which he was so careful to warn his audience. I have not had an opportunity to test the two substances, but it seems regrettable that such a beautiful histologic method should be lost; perhaps some one else may be stimulated to develop for it more certain rules of procedure.

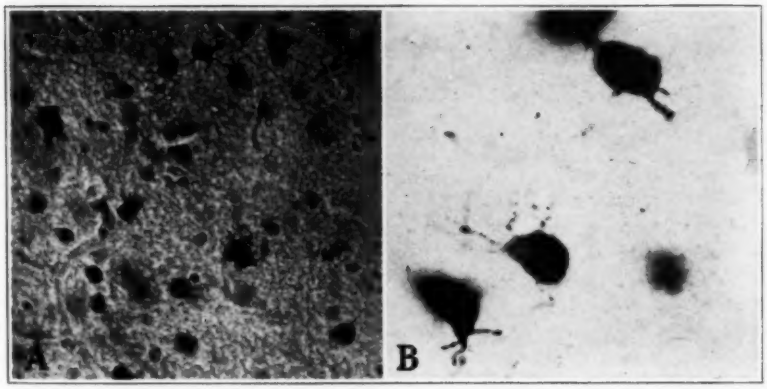


Fig. 1.—Photomicrographs from Robertson's original preparations showing the "mesoglia". A, × 300; B, × 850.

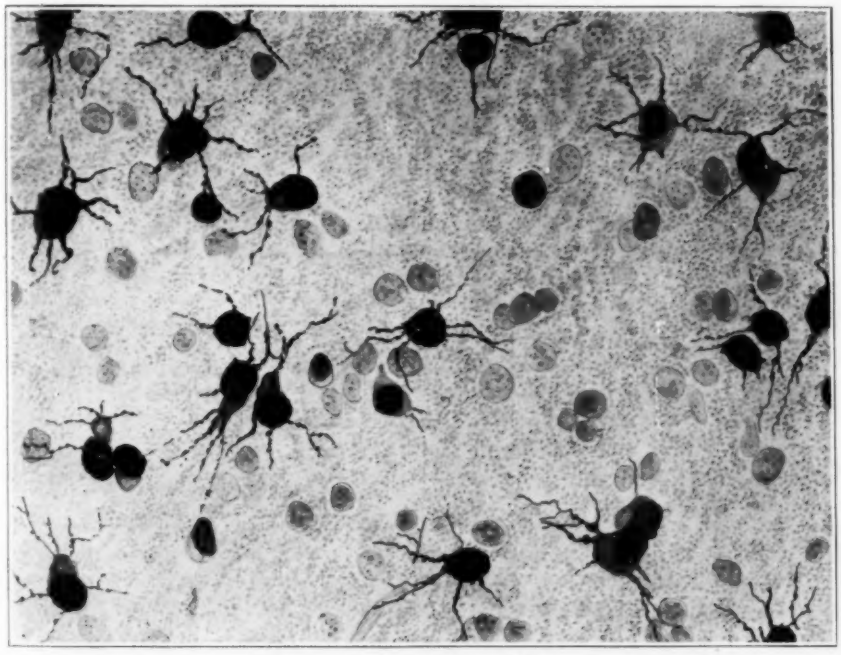


Fig. 2.—Drawing from one of Robertson's original preparations showing the details of the structure of the oligodendroglia (Robertson's mesoglia) in the dog.

Book Reviews

LES TROUBLES MENTAUX DANS LES TUMEURS CÉRÉBRALES. By HENRI BARUK. Price, 50 francs. Pp. 396. Paris: Gaston Doin, 1926.

This book contains a clinical study of fifty-five cases of cerebral tumor, of which fifteen showed serious disturbances and twenty-six mild disturbances. When analyzed by a psychiatrist, this proportion is probably not too high. It seems as though the author must have lived with the patients he studied, so detailed is the manner in which the reactions are presented and the patient's condition described in its changes from day to day. He points out also that recent methods of study and treatment in such cases offer new suggestions as to the pathogenesis of mental disorders. As far as localization goes, few signs can be relied on, and certain disorders are common to all types of tumors and to tumors in all locations. It seems to be a fact that the mental disorders are not constant; they change from day to day; simple confusion may give way to greater mental activity under stress.

In attempting to define the mental disorders characteristic of cerebral tumor, one must take account of the intracranial hypertension, because this is frequent and brings about a state of confusion that makes it somewhat difficult to get below the surface. In the long-standing case, likewise, there is a general reduction in mental capacity, often with a tendency to somnolence that leaves the examiner in great difficulties, because the patients often will not reply to questions even when repeated many times. The confused state runs practically parallel to intracranial hypertension, and may be removed from the picture by decompression, sometimes by spinal puncture or by the use of hypertonic saline solution. Under these circumstances, the underlying mental defect becomes more evident.

In the cases of mild form, slowing of intellectual operations is frequent. Memory for remote events is good, but memory for recent events is often affected. This seems to be due in large part to defect in the spontaneous attention as compared with the conservation of voluntary attention. As one patient said: "I remember only that which I determine to remember." These patients can concentrate attention for only a short time. Some of them live their former life over again, as in a dream, and recent and remote memories appear on the same plane. This gives rise sometimes to fantasy which, however, resembles considerably a normal dream, except that it takes place in the waking state.

Pathologic somnolence, which is distinguished from torpor or coma by the ease with which the patient is aroused, is often present and may be associated with a certain kind of loss of memory and confabulation. Such phenomena can be seen particularly in tumors affecting the infundibular region, and probably this is not a simple manifestation of intracranial hypertension. Such patients then suffer from inhibition of mental activity rather than from loss, and on being roused can comport themselves fairly well. They realize their defects. They are subjects of psychic impotence. Major psychiatric symptoms, such as hallucinations, delusions, anxiety states and manic episodes, are more rarely found. Cases of brain tumor, however, may be mistaken for dementia paralytica, Korsakoff psychosis or dementia praecox.

Symptoms more peculiar to cases of brain tumor are puerility and moria. In the first there seems to be something of a simple return to the infant level minus the intensity of impressions and the curiosity of the child. Euphoria usually appears only when headaches have stopped. Moria is particularly evident in cases of tumor of the frontal lobe.

In considering the nature of the mental disturbance in these cases, one must take account of the fundamental psychic processes of the patient. Those paranoid by nature will have a psychosis tinged strongly by paranoid features. Detailed psychologic and psychometric data that indicate which psychologic mechanisms were disturbed are given. In the summary, the author states that there is difficulty and slowing of all intellectual functions, particularly of association and evocation of images. There is marked diminution of spontaneous attention.

Automatic and spontaneous functions seem to be more affected than the superior functions of reasoning, logic and voluntary attention. These may compensate to some degree for the loss of automatism. All activity of the patient, even in its smallest detail, demands effort, but this exhausts the patient quickly and such exhaustion brings about lowering of the intellectual function. In spite of this, the patients rarely have an aspect of dementia. "Their perception, judgment, critical sense, superior faculties, are relatively intact. Their troubles are due to a difficulty of expression rather than to a veritable disorganization of psychic life." Disturbances in the affective sphere are usually superficial, in spite of the external appearance. The patients are often more affected in their means of expression than in the detail of their inner organization.

Psychosensory disturbances are more likely to enter into the category of hallucinoses because of the insight of the patients. "This heroic struggle between reason and madness again shows us how superficial the mental disorders are, almost exterior, and how they affect rather infrequently the personality of the subject. Visual hallucinations seem to coincide with waves of intracranial hypertension and are very significant of temporal lobe lesions if they occur in the hemianopic blind field."

Language is often affected, a peculiar monotony of intonation being noted, and, in addition to ordinary aphasia, one occasionally finds forgetfulness or difficulty in the identification of words, particularly those united by a hyphen. Slowness and a peculiar stilted expression are observed when tumors of the frontal lobe are present.

Mental symptoms are most frequent in tumors of the frontal lobe, and when the confusional state and other manifestations of intracranial hypertension are removed, the basic disturbances may appear. They are often early in onset, and in these tumors of the frontal lobes is found the greatest mental weakening, aside from hypertension. Mental symptoms combined with euphoria and moria with puerility are almost diagnostic. The same symptoms, however, are likely to be found in cases of tumor of the corpus callosum. Nevertheless, there is less tendency to facetiousness and more often a bizarre behavior of patients in handling objects, so-called "ideomotor apraxia" of the left side.

Tumors of the hypophysis, infundibulum, third ventricle, basal ganglia and mesencephalon are considered together because of the similarity of the symptoms produced. Disturbance in sleep is characteristic together with slowing of mental processes. The region of the parietotemporo-occipital lobes is the great receiving center for all sensory impressions. Therefore, one more often finds disturbances in the psychosensory functions. Disturbances of language are

more often found in tumors of this region (left side) than in those of any other area. Melancholia seems to be particularly frequent in lesions of the parietal lobe. Hallucinations occur in tumors of this region, particularly in those of the temporosphenoidal lobe. Tumors of other regions of the brain, particularly of the posterior fossa, usually produce symptoms through intracranial hypertension and not through direct disturbance of the cerebrum.

In the pathogenesis of mental symptoms in brain tumor, one must take account first of the localization and next of the inflammatory reaction, the compression brought about by the neoplasm and the cerebral intoxication. In cases in which simple intracranial hypertension was intense but existed for only a short time, the disturbance in cellular morphology was minimal. Such things, however, as sudden swelling, great compression and roentgenotherapy bring about severe edema. Widespread infiltration of certain tumors may explain the mental disturbance.

The author does not take into account the disturbance in circulation due to intracranial hypertension. This would seem to be of primary importance. Without speaking of the hemic circulation, he admits, however, that intracranial hypertension seems to constitute one of the most important elements in the pathogenesis of mental disorder. The torpor in cases of cerebral edema may be due to dilatation of the third ventricle during simple hypertension. Hallucinations seem to be due to direct involvement of the sensory pathways, peripheral or central, by the tumor but at other times are linked up with dreamy states and disorders of sleep. They may depend on intracranial hypertension alone. The author finds that the mental disorders in general are not correlated with the size of the tumor, but more often with the location.

In conclusion the author sums up his previous work in some direct and useful statements. "Psychodiagnosis" of tumor of the brain presents the following points: early appearance of serious mental weakness speaks in favor of tumor of the frontal lobes or corpus callosum. Puerility, euphoric excitement and moria are important second symptoms. Characteristic disturbances of sleep and disorder in the psychic regulation are in favor of a tumor at the base. Psychosensory disturbances, hallucinations, disorders based on aphasia, agnosia and apraxia, are seen particularly in tumors of the parietotemporooccipital region.

THE INTERNAL SECRETIONS OF THE SEX GLANDS. THE PROBLEM OF THE "PUBERTY GLAND." ALEXANDER LIPSCHUTZ, M.D., Professor of Physiology, Dorpat University (Esthonia). Price, $6.00. Pp. 513, with 140 Illustrations. Baltimore: Williams & Wilkins Company, 1924; Cambridge, England: W. Heffer & Sons, Ltd.

This rather lengthy book covers thoroughly the subject of the internal secretions of the sex glands. The subject matter is treated largely from the laboratory and experimental standpoint. However, it forms a solid basis for clinical interpretation and possibly for therapy. The book is commended because of the free use the author has made of comparative anatomy and physiology. There is a great deal of repetition in the text, and sometimes the author seems to be somewhat circumlocutory for the general reader. A concise summary at the end of each chapter would be a distinct advantage.

In the beginning of the book, the author formulates four questions concerning sexual characters, and these he answers in the remainder of the book. The first chapter is concerned with sexual dimorphism and the secondary

characters. Then the author considers the subject of castration; he shows that castrated males and females approach a common type but do not assume the characters of the opposite sex. An attempt to correlate the sexual phenomena of insects with those of man meets with somewhat indifferent success.

The chapter on the internal secretion of the sexual glands takes up the subject of transplantation, and the author concludes that successful transplantations are much more talked about than unsuccessful, and that there is therefore much more to be written on this phase of the subject. He also concludes that heterotransplantations may be successful, though they are much more difficult to "take." Ovarian grafts are much more likely to be successful than testicular. Testicular transplantation, however, is feasible and therapeutically sound. The question of the influence of the sex glands on sex character through internal secretions is raised, and the subject of nervous influence is discussed, but no definite conclusions are reached. The feeding of sex glands is still in the experimental stage, and the hypodermic administration of testicular and ovarian substance has given varied results.

In the chapter on histology of the testes, the rôle played by the interstitial cells is considered carefully. The author concludes that the preponderance of evidence is in favor of the interstitial cells of Leydig being the endocrine organ controlling sex. Of interest to the roentgenologist is the careful work on the effect of roentgen rays on the sex glands. It is shown clearly that there is degeneration of the seminiferous tubules but not of the cells of Sertoli or the interstitial cells, and that potency and sexual characters are not affected. A discourse is given on hypertrophy of the interstitial cells, and the author concludes rather generally that there is an hypertrophy when the seminiferous tubules degenerate. Full development of the sexual characteristics is apparently in no way dependent, however, on the amount of interstitial tissue. The supply of blood to the testes probably has a larger influence on hypertrophy of the interstitial cells than any other factor.

The phases of puberty and eunuchoidism in the male are taken up at great length. The author states: "Eunuchoidism may occur in the presence of full spermatogenesis, and a normal development of sexual characters may be brought about by testicular tissue when the tubules are in an infantile stage but where the interstitial cells are of the adult type." The effect of alcohol, other poisons and chronic disease is considered, and it is shown that these agencies produce degeneration of seminiferous tubules but apparently not of the interstitial cells. Degeneration also occurs after thyroidectomy.

Chapter V, on the internal secretion of the ovaries, is of interest mainly to the gynecologist. The author concludes that the internal secretion is produced partly by the cells of the membrana granulosa and partly by the theca interna. A chapter dealing with sex specific action of the testicular and ovarian hormones is based largely on experimental work. The isolation of these sex specific hormones is considered difficult because of the mode of preparation. The author is somewhat contradictory when he states that there is "a probability that different parts of the testicle and the ovary are involved in the endocrine functions of these organs in different ways." The seminal vesicles and the prostate gland, in their relation to the development of sex characters, possibly function only in the production of a diluent and an alkalizing medium necessary to the life of the spermatozoa.

The last four chapters deal with intersexuality, sexual precocity, sexual hormones and morphogenesis, and the problem of rejuvenation. Some interesting light is thrown on the subject of hermaphroditism. These chapters present

more practical material from the clinical standpoint than any of the preceding ones and are worth reading in their entirety.

In general, the book presents a thorough review of the subject of the sex glands. The literature is well covered. In many instances, when the reports are contradictory, the author has made experiments in his own laboratory and gives his results with conclusions, but always leaves an opportunity for the reader to form his own opinions. There is an excellent bibliography at the end of each chapter. On the whole, the book is carefully and logically arranged; it should be of particular interest to the experimenter, the neurologist and the internist.

LEITFADEN DER NEUROLOGISCHEN DIAGNOSTIK. By KURT SINGER. Price, 9 marks; bound, 11.40 marks. Pp. 242. Berlin: Urban & Schwarzenberg, 1926.

This small book of 242 pages covers the entire realm of neurology and psychiatry from the standpoint of differential diagnosis and, of necessity, the treatment of the various subjects is cursory. This is the second edition. The subject is approached from the standpoint of symptoms. There are nineteen divisions. For example, the neuroses are discussed in ten pages, pupillary disturbances in seven, dizziness in eight, tremors in eight, disturbances of gait in ten, and so on.

It is interesting to note that the motor disturbances are discussed under the following separate headings: paralyses, which are divided into peripheral and central disturbances; dystrophies and myasthenic reactions; muscle atrophies; disturbances in reflexes; disturbances in gait; twitchings; cramps and tremors, not to mention speech and eye paralyses, which are discussed separately.

The book is obviously written for the general practitioner and the student, and for the purpose intended is adequate.

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